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> d his
     (FILE 'USPAT' ENTERED AT 14:33:00 ON 12 SEP 95)
L1         23082 S "L1"
L2           190 S HPV OR PAPILLOMAVIRUS
L3            20 S L1 AND L2
=> d l3 1-20
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1. 5,447,839, Sep. 5, 1995, Detection of human **papillomavirus** by the polymerase chain reaction; M. Michele Manos, et al., 435/5, 6, 91.2; 436/501; 536/23.1, 24.3, 24.31, 24.32, 24.33; 935/77, 78, 88 [IMAGE AVAILABLE]

2. 5,437,951, Aug. 1, 1995, Self-assembling recombinant **papillomavirus** capsid proteins; Douglas R. Lowy, et al., 435/69.1, 252.3, 320.1; 530/350, 403; 536/23.72 [IMAGE AVAILABLE]

3. 5,415,995, May 16, 1995, Diagnostic peptides of human papilloma virus; Gary K. Schoolnik, et al., 435/7.1, 7.36, 236; 514/12; 530/324, 326, 327, 328 [IMAGE AVAILABLE]

4. 5,411,857, May 2, 1995, Probes for papillomaviruses and an in vitro diagnostic procedure for papilloma infections; Sylvie Beaudenon, et al., 435/5, 6; 536/23.72 [IMAGE AVAILABLE]

5. 5,401,627, Mar. 28, 1995, Antibodies to human **papillomavirus** latent proteins, diagnostic systems and methods; Joakim Dillner, et al., 435/5, 240.27; 436/518, 548; 530/387.9, 388.3, 389.4 [IMAGE AVAILABLE]

6. 5,364,758, Nov. 15, 1994, Primers and process for detecting human **papillomavirus** genotypes by PCR; Christophorus J. Meijer, et al., 435/5, 6, 91.2; 536/24.32, 24.33; 935/78 [IMAGE AVAILABLE]

7. 5,346,811, Sep. 13, 1994, Method and products for human **papillomavirus** detection; Ivan Galindo-Castro, et al., 435/5, 6; 530/387.1; 536/24.32 [IMAGE AVAILABLE]

8. 5,342,930, Aug. 30, 1994, Isolated DNA of human **papillomavirus** type 54(HPV54); Gerard Orth, et al., 536/23.72; 435/172.3, 320.1; 536/24.32 [IMAGE AVAILABLE]

9. 5,334,515, Aug. 2, 1994, Method for altering a nucleotide sequence; Ayoub Rashtchian, et al., 435/91.2, 91.41, 91.51, 172.3, 227 [IMAGE AVAILABLE]

10. 5,283,171, Feb. 1, 1994, Compositions for and detection of human **papillomavirus** by specific oligonucleotide polymerase primers using the polymerase chain reaction; M. Michele Manos, et al., 435/5, 6, 810; 436/501, 811; 536/23.1, 24.3, 24.31, 24.32, 24.33; 935/3, 20, 77, 78, 88 [IMAGE AVAILABLE]

11. 5,194,370, Mar. 16, 1993, Promoter ligation activated transcription amplification of nucleic acid sequences; Mark S. Berninger, et al., 435/6, 91.21; 436/94, 501; 935/77, 78 [IMAGE AVAILABLE]

12. 5,182,377, Jan. 26, 1993, Probes for detection of human **papillomavirus**; M. Michele Manos, et al., 536/24.32; 435/5, 6; 436/501, 811; 536/24.33; 935/3, 20, 77, 78 [IMAGE AVAILABLE]

13. 5,180,806, Jan. 19, 1993, Polypeptides and compositions of human **papillomavirus** latent proteins, diagnostic systems and methods; Joakim Dillner, et al., 530/326, 324, 325 [IMAGE AVAILABLE]

14. 5,169,766, Dec. 8, 1992, Amplification of nucleic acid molecules; David M. Schuster, et al., 435/91.2, 6, 91.21, 193, 194 [IMAGE AVAILABLE]

15. 5,057,411, Oct. 15, 1991, Type-specific **papillomavirus** DNA sequences and peptides; Wayne D. Lancaster, et al., 435/6, 5; 436/501, 811; 536/23.72, 24.32; 935/78 [IMAGE AVAILABLE]

16. 5,045,447, Sep. 3, 1991, Method of producing antibodies to **HPV**; Anthony C. Minson, 435/5; 422/61; 435/7.92; 436/548; 935/110 [IMAGE AVAILABLE]

17. 4,983,728, Jan. 8, 1991, Nucleic acid probes of human papilloma virus; Albert Herzog, et al., 435/5, 91.2, 948; 436/501, 811; 536/23.72, 24.32; 935/9, 16, 17, 78, 88 [IMAGE AVAILABLE]

18. 4,886,741, Dec. 12, 1989, Use of volume exclusion agents for the enhancement of in situ hybridization; Dennis E. Schwartz, 435/5, 6, 21, 810; 436/501; 935/77, 78 [IMAGE AVAILABLE]

19. 4,777,239, Oct. 11, 1988, Diagnostic peptides of human papilloma virus; Gary K. Schoolnik, et al., 530/326, 327, 328, 387.9, 389.4, 389.7, 389.8, 391.3; 930/220, DIG.811 [IMAGE AVAILABLE]

20. 4,551,270, Nov. 5, 1985, DNA Fragments coding for polypeptides containing at least one antigenic determinant of the **papillomavirus**, particularly of the **HPV** 1a type and corresponding polypeptides; Olivier Danos, et al., 530/327, 329; 930/220, DIG.811 [IMAGE AVAILABLE]

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US PAT NO: 5,437,951 [IMAGE AVAILABLE] L3: 2 of 20
DATE ISSUED: Aug. 1, 1995
TITLE: Self-assembling recombinant **papillomavirus** capsid proteins
INVENTOR: Douglas R. Lowy, Washington, DC
John T. Schiller, Silver Spring, MD
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ASSIGNEE: The United States of America as represented by the Department of Health and Human Services, Washington, DC (U.S. govt.)
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US-CL-ISSUED: 435/69.1, 252.3, 320.1; 530/350, 403; 536/23.72
US-CL-CURRENT: 435/69.1, 252.3, 320.1; 530/350, 403; 536/23.72
SEARCH-FLD: 435/69.1, 252.3, 320.1; 536/23.72; 530/350, 403
REF-CITED:

U.S. PATENT DOCUMENTS

4,520,113	5/1985	Gallo et al.	436/504
4,551,270	11/1985	Danos et al.	536/23.72
4,748,109	5/1988	Baird	435/5
4,777,239	10/1988	Schoolnik et al.	530/326
4,983,728	1/1991	Herzog et al.	536/24.32

5,039,607	8/1991	Skold et al.	435/7.5
5,045,447	9/1991	Minson	435/5
5,057,411	10/1991	Lancaster et al.	435/6
5,071,757	12/1991	Kreider et al.	435/236
5,081,029	1/1992	Zarling et al.	435/172.3
5,180,806	1/1993	Dillner et al.	530/326
5,186,933	2/1993	Estes	424/89

FOREIGN PATENT DOCUMENTS

9010459	9/1990	World Intellectual Property Organization
9118118	11/1991	World Intellectual Property Organization
9302184	2/1993	World Intellectual Property Organization

OTHER PUBLICATIONS

Hagensee, M. E. et al., 1993, Journal of Virology, 67(1):315-322.

Kirnbauer, R., et al., 1993, in Vaccines '.SIGMA., Ginsberg, H. S., et al., Eds. Cold Spring Harbor Laboratory Press, pp. 305-310.

Campo, M. S., et al., 1993, The Journal of General Virology, 74(6): 945-953.

Watson, J. D., et al., Eds., 1983, Recombinant DNA--A Short Course, p. 236, W. H. Freeman and Company (New York); publishers.

Kirnbauer R., et al., 1993, Journal of Virology, 67(12):6929-6936.

Sasagawa, T., et al., 1994, Programme and Abstract Book, 13th International Papillomavirus Conference, p. 154.

Kirnbauer, R., et al., 1994, Journal of The National Cancer Institute 86(7):494-499.

Editorial, Galloway, D. A., 1994, Journal of the National Cancer Institute, 86(7):474-475.

Carter, J. J., et al., 1991, Virology, 182:513-521.

Zhou, J., et al., 1992, Virology, 189(2):592-599.

Rose, R. C., et al., 1990 Journal of General Virology 71(11):2725-2729.

Steele, J. C., et al., 1990, Virology 174(2):388--398.

Cason, J., et al., 1992, International Journal of Cancer, 50(3):344-355.

Beiss, K. K., et al. 1991, Virology 184(1):460-464.

Lehtinen, M., et al., 1990, Biochemical and Biophysical Research Communications, 172(3):1378-1383.

Yaegashi, N., et al., 1991, Journal of Virology, 65(3):1578-1583.

Ghim, S.-J., et al., 1992, Virology, 190(1):548-552.

"Immunotherapeutic Products Will Have $2.4 Billion European Market in 1995", 1992, Biotechnology News, 12(8):2.

Kirnbauer, R., et al., 1992, Proceedings of the National Academy of Sciences, U.S.A., 89:12180-12184.

Baker, C. Sequence Analysis of Papillomavirus Genomes. The Papillomaviruses. 321-385 (1987).

Baker, T., et al., Structures of bovine and human papillomaviruses. Biophys. J. 60:1445-1456 (1991).

Bradley, L., et al., Selected methods in cellular immunology. In Vitro Immune Responses. 164-166 (1980).

Chen, E., et al. The primary structure and genetic organization . . . Nature. 299:529-534 (1982).

Christensen, N., et al. Monoclonal antibody-mediated neutralization of . . . J. of Virology. 64:5678-5687 (1990).

Christensen, N., et al. The open reading frame L2 of cottontail rabbit papillomavirus . . . Virology. 181:572-579 (1991).

Cowsert, L., et al. Topographical and conformational epitopes of bovine . . . J. Natl. Cancer Inst. 79:1053-1057 (1987).

Crawford, L., et al. A comparative study of polyoma and papilloma viruses. Virology 21:258-263 (1963).
Dvoretzky, I., et al., A quantitative in Vitro focus assay for bovine papilloma virus. Virology 103:369-375 (1980).
Ghim, S., et al., Comparison of neutralization of BPV-1 infection of C127 cells and . . . Int. J. Cancer 49:285-289 (1991).
Hartig, P. Generation of recombinant baculovirus via liposome-mediated trasnfection. Biotechniques 11:310-312 (1991).
Hopfl, R., et al., Skin test for HPV type 16 proteins in cervical intraepithelial . . . Lancet 337:373-374 (1991).
Jarrett, W., et al., Studies on vaccination against papillomaviruses . . . Veterinary Record 126:449-452 (1990).
Jarrett, W., et al. Studies on vaccination against papillomaviruses . . . Virology 184:33-42 (1991).
Jenison, S., et al. Evidence of prevalent genital-type human papillomavirus infections . . . J. Infectious Dis. 162:60-69 (1990).
Jenson, A., et al. Identification of linear epitopes of the BPV-1 L1 protein . . . Pathobiology 59:396-403 (1991).
Jin, X., et al., Identification of L2 open reading frame gene products of bovine . . . J. Gen. Virology 70:1133-1140 (1989).
Kajigaya, S., et al. Self-assembled B19 parvovirus capsids, produced in a baculovirus . . . Proc. Natl. Acad. Sci. USA 88:4646-4650 (1991).
Larsen, P., et al. Proteins present in bovine papillomavirus particles. virology 61:3596-3601 (1987).
Liddington, R., et al. Structure of simian virus 40 at 3.8-A resolution. Nature 354:278-284 (1991).
Lin, Yi, et al., Effective vaccination against papilloma development by immunization . . . Virology 187:612-619 (1992).
McLean, C., et al., Production and characterisation of a monoclonal antibody . . . J. Clin. Pathol. 43:488-492 (199).
Nakai, Y., et al. Monoclonal antiobides to genus- and type-specific papillomavirus . . . Intervirol. 25:30-37 (1986).
Olson, C., et al. Further observations on immunity to bovine cutaneous papillomatosis. Amer. J. Vet. Res. 21:233-242 (1960).
Pilacinski, W., et al. Immunization against bovine papillomavirus infection. Biotechnology 2:136-156 (1984).
Saiki, R. K. et al. Primer-directed enzymatic amplification of DNA with a thermostable . . . Science 239:487-491 (1987).
Schiffman, M., et al. Recent progress in defining the epidemiology of human papillomavirus . . . National Cancer Inst. 84:394-398 (1992).
Seedorf, K., et al. Human papillomavirus type 16 DNA sequence. Virology 145:181-185 (1985).
Stevens, C., et al. Yeast-recombinant hepatitis B vaccine. JAMA 257:2612-2616 (1987).
Stites, D. et al. Clinical laboratory methods of detecting cellular immune function. Basic and Clinical Immunology 3:382-397 (1980).
Summers, D., et al. A manual of methods of baculovirus vectors and insect cell culture . . . Bulletin No. 1555, Texas A & M University, 1988.
Zhou, J. et al. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells . . . J. Virology 185:251-257 (1991).
Zur Hausen, H. Viruses in human cancers. Science 254:1167-1173 (1991).
Wang, X., et al. Baculovirus vectors for multiple gene expression and for occluded . . . Gene 100:131-137 (1991).
Browne, H. M., et al. Analysis of the L1gene product of human papillomavirus type 16 by . . . J. Gen. Virol. 69:1263-1273 (1988).
Davies, D. H., et al. Definition of murine T helper cell determinants in the major capsid . . . J. Gen. Virol. 71:2691-2698 (1990).
Jenkins, O., et al. An antigen chimera of poliovirus induces antibodies

against . . . J. of Virology 1201-1206 (199).
Montross, L., et al. Nuclear assembly of polyomavirus capsids in insect cells . . . J. of Virology 4991-4998 (1991).
Zhou, J., et al. The induction of cytotoxic T-Lymphocyte precursor cells by recombinant . . . Virology 181:203-210 (1991).
Zhou, J., et al. Increased antibody responses to human papillomavirus type 16 L1 protein . . . J. of Gen Virology 71:2185-2190 (1990).
Zhou, J. et al., Identification of the nuclear localization signal of human papillomavirus . . . Virology 185:6267-632 (1991).
Xi, et al., "Baculovirus expression of the human papillomavirus type 16 capsid proteins detection of L1-L2 protein complexes," Journal of General Virology, vol 72, No. 12, Dec. 1991, pp. 2981-2988.
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ABSTRACT:
Recombinant **papillomavirus** capsid proteins that are capable of self-assembly into capsomer structures and viral capsids that comprise conformational antigenic epitopes are provided. The capsomer structures and viral capsids, consisting of the capsid proteins that are expression products of a bovine, monkey or human **papillomavirus** **L1** conformational coding sequence proteins, can be prepared as vaccines to induce a high-titer neutralizing antibody response in vertebrate animals. The self assembling capsid proteins can also be used as elements of diagnostic immunoassay procedures for **papillomavirus** infection.
23 Claims, 3 Drawing Figures

US PAT NO: 5,437,951 [IMAGE AVAILABLE] L3: 2 of 20
TITLE: Self-assembling recombinant **papillomavirus** capsid proteins

ABSTRACT:
Recombinant **papillomavirus** capsid proteins that are capable of self-assembly into capsomer structures and viral capsids that comprise conformational antigenic epitopes are provided.. . . capsomer structures and viral capsids, consisting of the capsid proteins that are expression products of a bovine, monkey or human **papillomavirus** **L1** conformational coding sequence proteins, can be prepared as vaccines to induce a high-titer neutralizing antibody response in vertebrate animals. The self assembling capsid proteins can also be used as elements of diagnostic immunoassay procedures for **papillomavirus** infection.

SUMMARY:

BSUM(1)

Papillomaviruses . . . or warts, at the site of infection. Each species of vertebrate is infected by a distinct group of papillomaviruses, each **papillomavirus** group comprising several **papillomavirus** types. For example, more than 60 different human **papillomavirus** (**HPV**) genotypes have been isolated. Papillomaviruses are highly species specific infective agents; for example, a bovine **papillomavirus** cannot induce papillomas in a heterologous species, such as humans. **Papillomavirus** types ALSO appear to be highly specific as immunogens in that a neutralizing

immunity to infection against one **papillomavirus** type does not usually confer immunity against another type, even when the types infect an homologous species.

SUMMARY:

BSUM(2)

In . . . which are caused by human papillomaviruses, represent a sexually transmitted disease. Genital warts are very common, and subclinical, or inapparent **HPV** infection is even more common than clinical infection. Some benign lesions in humans, particularly those arising from certain **papillomavirus** types, undergo malignant progression. For that reason, infection by one of the malignancy associated papilloma virus types is considered one. . . of cervical cancer, the second most common cancer of women worldwide (zur Hausen, H., 1991; Schiffman, M. 1992). Several different **HPV** genotypes have been found in cervical cancer, with HPV16 being the most common type that is isolated from 50% of. . .

SUMMARY:

BSUM(3)

Immunological studies demonstrating the production of neutralizing antibodies to **papillomavirus** antigens indicate that **papillomavirus** infections and malignancies associated with these infections in vertebrate animals could be prevented through immunization; however the development of effective **papillomavirus** vaccines has been impeded by a number of difficulties.

SUMMARY:

BSUM(4)

First, . . . possible to generate in vitro the large stocks of infectious virus required to determine the structural and immunogenic features of **papillomavirus** that are fundamental to the development of effective vaccines. Cultured cells express **papillomavirus** oncoproteins and other non-structural proteins and these have been extensively studied in vitro; but expression of the structural viral proteins, **L1** and L2 (and the subsequent assembly of infectious virus) occurs only in terminally differentiated layers of infected epithelial tissues. Therefore,. . . characterization of viral genes, proteins, and structure has necessarily been assembled from studies of virus harvested from papillomas. In particular, **papillomavirus** structure and related immunity have been carried out in the bovine **papillomavirus** system because large amounts of infectious virus particles can be isolated from bovine **papillomavirus** (BPV) warts.

SUMMARY:

BSUM(5)

The information derived from studies of **papillomavirus** structure to date indicates that all papillomaviruses are non-enveloped 50-60 nm icosahedral structures (Crawford, L., et al., 1963) which are comprised of conserved **L1** major capsid protein and less well conserved L2 minor

capsid protein (Baker, C., 1987). There is no sequence relationship between. . . and location of L2 in the capsid is unclear; however immunologic data suggests that most of L2 is internal to **L1**.

SUMMARY:

BSUM(6)

Recently, . . . determined that the two viruses have a very similar structure, with 72 pentameric capsomers, each capsomer presumably composed of five **L1** molecules, forming a virion shell with T=7 symmetry (Baker, T., 1991). The location of the minor L2 capsid protein in. . . not been determined, and it is not certain whether L2 or other viral proteins are needed for capsid assembly. Superficially, **papillomavirus** structure resembles that of the polyoma 45 nm virion, which has the same symmetry and capsomere number (Liddington, R., et al., 1991); however, the systems of intracapsomer contact for polyomavirus and **papillomavirus** species are different, and the major and minor capsid proteins of polyomavirus are not genetically related to **L1** and L2.

SUMMARY:

BSUM(7)

Bovine **papillomavirus** studies are facilitated by a quantitative focal transformation infectivity assay developed for BPV that is not available for **HPV** (Dvoretzky, I., et al., 1980), and an understanding of immunity to **papillomavirus** has therefore also been derived from the bovine **papillomavirus** system. Limited studies using intact bovine **papillomavirus** demonstrated that the non-cutaneous inoculation of infectious or formalin-inactivated BPV virus was effective as a vaccine to prevent experimental BPV. . . (Olson, C., et al., 1960; Jarrett, W., et al., 1990). Unfortunately, BPV virions cannot be used to develop vaccines against **papillomavirus** which infects other species, or even vaccines against other bovine types, because of the great specificity of these viruses, as. . .

SUMMARY:

BSUM(8)

A significant conclusion of studies of **papillomavirus** immunity is that the ability of antibodies to neutralize papilloma virus appears to be related to their ability to react. . .

SUMMARY:

BSUM(9)

In contrast, neutralizing sera generated against bacterially derived BPV **L1** and L2 (Pilacinski, W. et al., 1984; Jin, X., et al., 1989) and against in vitro synthesized cottontail rabbit **papillomavirus** (CRPV) **L1** and L2 (Christensen, N., et al., 1991; Lin, Y -L, et al., 1992), neither of which has the structural features of native virions, had low titers, and the use of recombinant **HPV** **L1** fusion peptides expressed in E. coli to detect cellular immune reactivity has had only limited success (Hopfl, R. et al., 1991). The results in the BPV system are consistent with those of the **HPV** system, in which monoclonal

antibodies that neutralized HPV11 infection in a mouse xenograft assay recognized native, but not denatured, HPV11. . .

SUMMARY:

BSUM(10)

There have been isolated attempts to produce **papillomavirus** capsids in vitro. Zhou, J. et al. (1991) and (1992) produced virus-like particles by cloning **HPV** **L1** and L2 genes, and **HPV** **L1** and L2 genes in combination with **HPV** E3/E4 genes into a vaccinia virus vector and infecting CV-1 mammalian cells with the recombinant vaccinia virus. These studies were interpreted by Zhou to establish that expression of HPV16 **L1** and L2 proteins in epithelial cells is necessary and sufficient to allow assembly of virion type particles. Cells infected with doubly recombinant vaccinia virus which expressed **L1** and L2 proteins showed small (40 nm) virus-like particles in the nucleus that appeared to be incompletely assembled arrays of **HPV** capsomers. Expressing **L1** protein alone, or L2 protein alone, was expressed did not produce virus-like particles; cells doubly infected with singly recombinant vaccinia virus containing **L1** and L2 genes also did not produce particles. No neutralizing activity was reported.

SUMMARY:

BSUM(11)

Ghim et al., (1992) reported that when **L1** from HPV1, a non-genital virus type associated mainly with warts on the hands and feet, was expressed in mammalian cells, the **L1** protein contained conformational epitopes found on intact virions. Ghim did not determine if particles were produced, nor was it evaluated if the **L1** protein might induce neutralizing antibodies. Even more recently, Hagansee, et al. (1993) reported that when **L1** from HPV1 was expressed in human cells, it self-assembled into virus-like particles. No neutralizing antibody studies were performed.

SUMMARY:

BSUM(13)

It would be advantageous to develop methods for producing renewable **papillomavirus** reagents of any selected species and type in cell culture. It would also be beneficial to produce such **papillomavirus** reagents having the immunity conferring properties of the conformed native virus particles that could be used as a subunit vaccine.

SUMMARY:

BSUM(14)

It is therefore the object of the invention to provide these recombinant conformed **papillomavirus** proteins, as well as methods for their production and use.

SUMMARY:

BSUM(16)

The invention is directed to the diagnosis and prevention of **papillomavirus** infections and their benign and malignant sequelae by providing recombinant **papillomavirus** capsid proteins that self assemble to form capsomer structures comprising conformational epitopes that are highly specific and highly immunogenic. Therefore, according to the invention there is provided a genetic construct, comprising a **papillomavirus** **L1** conformational coding sequence, inserted into a baculovirus transfer vector, and operatively expressed by a promoter of that vector. The **papillomavirus** **L1** conformational coding sequence can be isolated from a bovine, monkey, or human gene. In a preferred embodiment, the **papillomavirus** **L1** conformational coding sequence is isolated from a wild type HPV16 gene. In a particularly preferred embodiment, the **papillomavirus** **L1** conformational coding sequence is Sequence ID No. 2. The genetic construct can further comprise a **papillomavirus** L2 coding sequence.

SUMMARY:

BSUM(18)

According to yet another aspect of the invention there is provided a method for producing a recombinant **papillomavirus** capsid protein, assembled into a capsomer structure or a portion thereof, comprising the steps of (1) cloning a **papillomavirus** gene that codes for an **L1** conformational capsid protein into a transfer vector wherein the open reading frame of said gene is under the control of the promoter of said vector; (2) transferring the recombinant vector into a host cell, wherein the cloned **papillomavirus** gene expresses the **papillomavirus** capsid protein; and (3) isolating capsomer structures, comprising the **papillomavirus** capsid protein, from the host cell. In a preferred embodiment, the cloned **papillomavirus** gene consists essentially of the conformational **L1** coding sequence, and the expressed protein assembles into capsomer structures consisting essentially of **L1** capsid protein. In another preferred embodiment, the cloning step of the method further comprises the cloning of a **papillomavirus** gene coding for L2 capsid protein, whereby said **L1** and L2 proteins are coexpressed in the host cell, and wherein the isolated capsomer structures comprise **L1** and L2 capsid proteins; provided that said transfer vector is not a vaccinia virus when said host cell is a mammalian cell. The conformational **L1** coding sequence can be cloned from a bovine, monkey, or human **papillomavirus**. According to a preferred embodiment, the conformational **L1** coding sequence is cloned from a wild type HPV16 **papillomavirus**. In a particularly preferred embodiment, the conformational **L1** coding sequence is Sequence ID No. 2. Also in a preferred embodiment, the host cell into which the genetic construct. . . is an insect cell. Also preferred are embodiments wherein the transfer vector is a baculovirus based transfer vector, and the **papillomavirus** gene is under the control of a promoter that is active in insect cells. Accordingly in this embodiment, the recombinant. . .

SUMMARY:

BSUM(20)

According . . . yet another aspect of the invention there is provided a virus capsomer structure, or a portion thereof, consisting essentially

of **papillomavirus** **L1** capsid protein, produced by the method the invention. Alternatively, the virus capsomer structure can consist essentially of **papillomavirus** **L1** and L2 capsid proteins, produced by the method of the invention. In a particularly preferred embodiment, the virus capsomer structure comprises **papillomavirus** **L1** capsid protein that is the expression product of an HPV16 **L1** DNA cloned from a wild type virus. The virus capsids or capsomer structures of the invention, or portions or fragments thereof, can consist essentially of **papillomavirus** **L1** capsid protein. Alternatively, these capsids or capsomer structures or their fragments can consist essentially of wild type HPV16 **papillomavirus** **L1** capsid protein.

SUMMARY:

BSUM(21)

The . . . of the methods of the invention comprise capsid proteins having immunogenic conformational epitopes capable of inducing neutralizing antibodies against native **papillomavirus**. The capsid proteins can be bovine, monkey or human **papillomavirus** **L1** proteins. In a preferred embodiment, the **papillomavirus** **L1** capsid protein is the expression product of a wild type HPV16 **L1** gene. In a particularly preferred embodiment, the HPV16 **L1** gene comprises the sequence of Sequence ID No. 2.

SUMMARY:

BSUM(22)

According . . . of the invention there is provided a unit dose of a vaccine, comprising a peptide having conformational epitopes of a **papillomavirus** **L1** capsid protein, or **L1** protein and L2 capsid proteins, in an effective immunogenic concentration sufficient to induce a **papillomavirus** neutralizing antibody titer of at least about 10.sup.3 when administered according to an immunizing dosage schedule. In a preferred embodiment, the vaccine comprises an **L1** capsid protein which is an HPV16 capsid protein. In a particularly preferred embodiment, the vaccine comprises an **L1** capsid protein that is a wild type HPV16 **L1** protein.

SUMMARY:

BSUM(23)

Use of the **L1** open reading frame (ORF) from a wild type HPV16 **papillomavirus** genome, according to the methods of the invention, particularly facilitates the production of preparative amounts of virus-like particles on a. . .

SUMMARY:

BSUM(24)

According to yet another aspect of the invention, there is provided a method of preventing or treating **papillomavirus** infection in a vertebrate, comprising the administration of a **papillomavirus** capsomer structure or a fragment thereof according to the invention to a vertebrate, according to an immunity-producing regimen. In a preferred

embodiment, the **papillomavirus** capsomer structure comprises wild type HPV16 **L1** capsid protein.

SUMMARY:

BSUM(25)

The invention further provides a method of preventing or treating **papillomavirus** infection in a vertebrate, comprising the administration of the **papillomavirus** capsomer structure of the invention, or a vaccine product comprising the capsomer structure to a vertebrate, according to an immunity-producing regimen. In a preferred embodiment, the **papillomavirus** vaccine comprises wild type HPV16 **L1** capsid protein.

SUMMARY:

BSUM(26)

Also within the scope of the invention is a method for immunizing a vertebrate against **papillomavirus** infection, comprising administering to the vertebrate a recombinant genetic construct of the invention comprising a conformational **papillomavirus** **L1** coding sequence, and allowing said coding sequence to be expressed in the cells or tissues of said vertebrate, whereby an effective, neutralizing, immune response to **papillomavirus** is induced. In a preferred embodiment, the conformational **papillomavirus** **L1** coding sequence is derived from human **papillomavirus** HPV16. In a particularly preferred embodiment, the human **papillomavirus** HPV16 is a wild type **papillomavirus**.

SUMMARY:

BSUM(27)

According to yet another aspect of the invention, there is provided a method of detecting humoral immunity to **papillomavirus** infection in a vertebrate comprising the steps of: (a) providing an effective antibody-detecting amount of a **papillomavirus** capsid peptide having at least one conformational epitope of a **papillomavirus** capsomer structure; (b) contacting the peptide of step (a) with a sample of bodily fluid from a vertebrate to be examined for **papillomavirus** infection, and allowing **papillomavirus** antibodies contained in said sample to bind thereto, forming antigen-antibody complexes; (c) separating said complexes from unbound substances; (d) contacting the complexes of step (c) with a detectably labelled immunoglobulin-binding agent; and (e) detecting anti-**papillomavirus** antibodies in said sample by means of the labelled immunoglobulin-binding agent that binds to said complexes. In a preferred embodiment of this aspect of the invention, the peptide consists essentially of **papillomavirus** **L1** capsid protein. According to an alternative embodiment, the peptide consists essentially of the expression product of a human **papillomavirus** HPV16. In a particularly preferred embodiment, the peptide consists essentially of the expression product of a wild type human **papillomavirus** HPV16 gene, for example, the peptide can consist essentially of the expression product of Sequence ID No. 2.

SUMMARY:

BSUM(28)

According to yet another aspect of the invention, there is provided a method of detecting **papillomavirus** in a specimen from an animal suspected of being infected with said virus, comprising contacting the specimen with antibodies having a specificity to one or more conformational epitopes of the capsid of said **papillomavirus**, wherein the antibodies have a detectable signal producing label, or are attached to a detectably labelled reagent; allowing the antibodies to bind to the **papillomavirus**; and determining the presence of **papillomavirus** present in the specimen by means of the detectable label.

SUMMARY:

BSUM(29)

According to yet another aspect of the invention, there is provided a method of determining a cellular immune response to **papillomavirus** in an animal suspected of being infected with the virus, comprising contacting immunocompetent cells of said animal with a recombinant wild type **papillomavirus** **L1** capsid protein, or combined recombinant **L1** and L2 capsid proteins according to the invention; and assessing cellular immunity to **papillomavirus** by means of the proliferative response of said cells to the capsid protein. In a preferred embodiment of this aspect of the invention, the recombinant **papillomavirus** protein is introduced into the skin of the animal.

SUMMARY:

BSUM(30)

According to yet another aspect of the invention there is provided a **papillomavirus** infection diagnostic kit, comprising capsomer structures consisting essentially of **papillomavirus** **L1** capsid protein, or capsomer structures comprising **papillomavirus** **L1** protein and L2 capsid proteins, or antibodies to either of these capsomer structures, singly or in combination, together with materials for carrying out an assay for humoral or cellular immunity against **papillomavirus**, in a unit package container.

DRAWING DESC:

DRWD(2)

FIG. 1 shows the expression of BPV **L1** and HPV16 **L1** by means of recombinant virus as demonstrated by SDS-PAGE analysis of lysates from infected insect cells.

DRAWING DESC:

DRWD(3)

FIG. 2 shows the conformation of purified recombinant BPV **L1** and HPV16 **L1** capsid proteins as demonstrated by electron microscopy, compared with authentic BPV virions.

DRAWING DESC:

DRWD(4)

FIG. 3 shows the titers of neutralizing antisera induced in animals inoculated with recombinant BPV **L1** as compared to antisera against intact and denatured BPV virions.

DETDESC:

DETD(2)

We have discovered that the gene coding for the **L1** major capsid protein of BPV or HPV16, following introduction into host cells by means of an appropriate transfer vector, can express **L1** at high levels, and that the recombinant **L1** has the intrinsic capacity to self-assemble into empty capsomer structures that closely resemble those of an intact virion.

DETDESC:

DETD(3)

Further, the self-assembled recombinant **L1** capsid protein of the invention, in contrast to **L1** protein extracted from recombinant bacteria, or denatured virions, has the efficacy of intact **papillomavirus** particles in the ability to induce high levels of neutralizing antiserum that can protect against **papillomavirus** infection. The high level of immunogenicity of the capsid proteins of the invention implies strong antibody binding properties that make. . . be used as highly effective vaccines or immunogens to elicit neutralizing antibodies to protect a host animal against infection by **papillomavirus**. These observations were recently published in Kirnbauer, et al., (1992), and formed the basis of U.S. application Ser. No. 07/941,371.

DETDESC:

DETD(4)

We have now discovered that the capsid protein **L1** expressed by wild type HPV16 genomes isolated from benign **papillomavirus** lesions, when expressed in the baculovirus system described, will self-assemble with an efficiency heretofore unknown and comparable to that of bovine papillovirus **L1** capsid protein.

DETDESC:

DETD(5)
The HPV16 **L1** Gene Sequences

DETDESC:

DETD(6)

The source of HPV16 **L1** DNA, as disclosed in published studies, for example, by Zhou, et al. (1991) was the prototype clone, GenBank Accession No. K02718, that had been isolated from a cervical carcinoma (Seedorf, et al., 1985). We have found that **L1** from wild type HPV16 genome, which differs from the prototype genome by a single point

mutation, will self-assemble into virus-like particles with an efficiency similar to that seen with BPV **L1** or BPV **L1**/L2. Compared with the self-assembly seen when **L1** from the prototype **HPV** genome is used with L2, **L1** from a wild-type genome self-assembles at least 100 times more efficiently.

DETDESC:

DETD(7)

To provide genetic insight into the self-assembly efficiency of different HPV16 **L1** expression products, the open reading frames from HPV16 **L1** genes isolated from both benign lesions and lesions associated with dysplasia or carcinoma were sequenced.

DETDESC:

DETD(8)

The analysis detected two errors in the published sequence of the published **L1** sequence of the prototype strain, as follows:

DETDESC:

DETD(9)
(1) . . . insertion of three nucleotides (ATC) between nt 6902 and 6903, which results in the insertion of a serine in the **L1** protein; and

DETDESC:

DETD(10)
(2) . . . deletion in the published prototype sequence of three nucleotides (GAT), consisting of nt 6952-6954, which deletes an aspartate from the **L1** protein sequence. The corrected nucleotide sequence of the prototype HPV16 **L1** genome, consisting of nt 5637-7155, is that of Sequence ID No. 1, listed herein.

DETDESC:

DETD(11)

The . . . in Sequence ID Nos. 1 and 2 is indexed to 1, and the numbering of nucleotide bases of the published **HPV** sequence, that is from nt 5638-7156, corresponds to those of the sequence listing from 1-1518. The sites referred to in. . .

DETDESC:

DETD(12)

Three other HPV16 **L1** genomes, clone 16PAT; and clones 114/16/2 and 114/16/11, were sequenced and those sequences compared to that of the corrected prototype.

DETDESC:

DETD(13)

Clone . . . at the University of Rochester School of Medicine, and cloned from a dysplastic (pre-malignant) lesion of the cervix, expresses an **L1** that does not self-assemble efficiently.

DETDESC:

DETD(14)

Clones . . . by Matthias Durst of the German Cancer Research Center in Heidelburg, were both cloned from non-malignant lesions, and both expressed **L1** protein that self-assembled efficiently.

DETDESC:

DETD(15)
Comparison of Genetic Characteristics of HPV16 **L1** associated with Dysplasia, Malignant Progression and Benign Lesions

DETDESC:

DETD(16)

Clone 16PAT, isolated from **papillomavirus** infected dysplastic lesions and the prototype HPV16, isolated from malignant cervical carcinoma, both encode Histidine at nt 6242-6244, while clones 2 and 11, isolated from benign **papillomavirus** infected lesions (like isolates of many other **papillomavirus**) encode Aspartate at this site.

DETDESC:

DETD(17)

It . . . the HPV16 species from benign lesions accounts for the difference in self-assembly efficiency. It is likely that among closely related **HPV** types, Aspartate at this locus may be necessary for efficient self-assembly, and that the substitution of Histidine for Aspartate impairs. . . epitopes required for the production of neutralizing antibodies, may also be linked to a lowered immunogenicity which would allow the **papillomavirus** to escape immune control.

DETDESC:

DETD(18)

Accordingly, HPV16 **L1** genes that express capsid protein that self-assembles efficiently can be obtained by (1) isolation of the wild type HPV16 **L1** open reading frame from benign lesions of **papillomavirus** infection; or (2) carrying out a site specific mutation in the prototype sequence at nt 6242-6244 to encode Aspartate.

DETDESC:

DETD(20)

The method of the invention provides a means of preparing recombinant capsid particles for any **papillomavirus**. Particles consisting of either **L1** or L2 capsid protein alone, or consisting of both **L1**

and L2 capsid proteins together can be prepared. **L1**/L2 capsid protein particles are more closely related to the composition of native **papillomavirus** virions, but L2 does not appear to be as significant as **L1** in conferring immunity, probably because most of L2 is internal to **L1** in the capsid structure. Although **L1** can self-assemble by itself, in the absence of L2, self-assembled **L1**/L2 capsid protein particles are more closely related to the composition of native **papillomavirus** virions. Accordingly, particles comprising **L1** alone are simpler, while those comprising **L1**/L2 may have an even more authentic structure. Both self-assembled **L1** and **L1**/L2 particles induce high-titer neutralizing antibodies and may therefore be suitable for vaccine production. Particles comprising **L1** capsid protein expressed by a wild type **HPV** genome, either as **L1** alone or **L1**/L2 together, are particularly preferred.

DETDESC:

DETD(21)

Production of the recombinant **L1**, or combined **L1**/L2, capsid particles is carried out by cloning the **L1** (or **L1** and L2) gene(s) into a suitable vector and expressing the corresponding conformational coding sequences for these proteins in a eukaryotic. . .

DETDESC:

DETD(22)

According . . . preferred protocol, a baculovirus system is used. The gene to be cloned, substantially all of the coding sequence for bovine **papillomavirus** (BPV1) or human **papillomavirus** (HPV16) **L1** capsid protein, or human **papillomavirus** HPV16 **L1** and L2, is inserted into a baculovirus transfer vector containing flanking baculovirus sequences to form a gene construct, and the. . . high levels. The actual production of protein is made by infecting fresh insect cells with the recombinant baculovirus; accordingly, the **L1** capsid protein and the **L1** and L2 capsid proteins are expressed in insect cells that have been infected with recombinant baculovirus as described in Example. . .

DETDESC:

DETD(23)

In the procedure of Example 1, the complete **L1** gene of BPV1 was amplified by polymerase chain reaction (PCR; Saiki, R., et al., 1987) and cloned into AcMNPV (Autographa californica nuclear polyhedrosis virus) based baculovirus vector (Summers, M. et al., 1987). The **L1** open reading frame was put under the control of the baculovirus polyhedrin promoter. After co-transfection of the **L1** clone with the wild type (wt) baculovirus DNA into Sf-9 insect cells (ATCC Accession No. CRL 1711) and plaque purification of recombinant clones, high titer recombinant virus was generated. Extracts from cells infected with wt AcMNPV or BPV1 **L1** recombinant viruses (AcBPV-**L1**) (Example 2) were analyzed by polyacrylamide gel electrophoresis. After Coomassie blue staining, a unique protein of the predicted size, 55 kilodaltons, was detected in extracts from the cultures infected with the AcBPV1-**L1** virus (FIG. 1A). The identity of this protein as BPV **L1** was verified by

immunoblotting (FIG. 1B), using a BPV **L1** specific monoclonal antibody (Nakai, Y., et al., 1986).

DETDESC:

DETD(24)

To test the hypothesis that **papillomavirus** **L1** has the ability to self-assemble into virus-like particles when overexpressed in heterologous cells, electron micrographs of thin sections from AcBPV-**L1** infected cells were examined for the presence of **papillomavirus**-like structures. Cells infected with the BPV recombinant virus contained many circular structures of approximately 50 nm which were preferentially localized. . . in the nucleus; these structures were absent from wild type baculovirus infected cells. These results suggested that self assembly of **L1** into virus-like particles had occurred, since in vivo **papillomavirus** virion assembly takes place in the nucleus and the diameter of the virions has been reported as 55 nm.

DETDESC:

DETD(25)

Following . . . virus particles are purified from lysates of infected cells as described in Example 4. To obtain further evidence that the **L1** protein had self-assembled, virus-like particles were isolated from the infected insect cells by means of gradient centrifugation (FIG. 2).

DETDESC:

DETD(26)

High molecular mass structures were separated from lysates of **L1** recombinant or wild type infected cells by centrifugation through a 40% sucrose cushion and the pelleted material was subjected to CsCl density gradient centrifugation. Fractions were collected and tested for reactivity to the BPV **L1** specific monoclonal antibody by immunoblotting.

DETDESC:

DETD(27)

L1 positive fractions from the gradient were adsorbed onto carbon film grids, stained with 1% uranyl acetate and examined by transmission. . . These particles were not observed in preparations from mock infected or wt AcMNPV infected cells. These results indicate that BPV **L1** has the intrinsic capacity to assemble into virus-like particles in the absence of L2 or other **papillomavirus** proteins. In addition, specific factors limited to differentiating epithelia or mammalian cells are not required for **papillomavirus** capsid assembly.

DETDESC:

DETD(28)

To determine if the ability to self-assemble in insect cells is a general feature of **papillomavirus** **L1**, we also expressed the **L1** of HPV16, the **HPV** type most often detected in human genital cancers, via an analogous recombinant baculovirus. A protein of the expected 58 kd size was expressed at high levels in the insect cells infected with the HPV16-**L1** recombinant virus (FIG. 1A) and it reacted strongly with an HPV16 **L1** monoclonal antibody (which also reacted weakly with BPV **L1**; FIG. 1C). After CsCl gradient purification, immunoreactive fractions were examined by electron microscopy and found to contain 50 nm **papillomavirus**-like particles (FIG. 2C). Although somewhat fewer completely assembled particles were seen in the human system in comparison to the BPV **L1** preparations, possibly due to the lower levels of expression or greater extent of HPV16 **L1** degradation (FIG. 1), the results conclusively indicate that the **L1** of the HPV16 and presumably the **L1** proteins of other types, have the intrinsic capacity to assemble into virion-type structures. Preparations of recombinant **papillomavirus** capsid particles for Rhesus monkey PV have also been carried out as described in the Examples.

DETDESC:

DETD(31)

Studies . . . viral capsid proteins, rather than early gene products, elicit the immune response. Other data in the scientific literature indicates that **L1** protein extracted from bacteria was partially successful in eliciting an immune response despite the low titers of neutralizing antibodies. Accordingly, the BPV **L1** that was expressed and assembled into virus-like particles in insect cells was studied for its ability to induce neutralizing antisera in rabbits. Two types of preparations were tested: whole cell extracts of **L1** recombinant or wild type infected Sf-9 cells and partially purified particles isolated by differential centrifugation and ammonium sulfate precipitation. Following. . .

DETDESC:

DETD(32)

The . . . of BPV virus (a representative assay is shown in FIG. 3). The immune sera generated by inoculation with baculovirus derived **L1** were able to reduce the infectivity of the BPV virus by 50% at a dilution of at least 1:11,000 (a. . . control antiserum raised against infectious BPV virions. In comparison, the highest titer generated in a previous study using bacterially derived **L1** was 36 (Pilancinski, W., et al., 1984). The serum from the rabbit inoculated with the extract from the wild type baculovirus infected cells was unable to inhibit infectivity at a dilution of 1:20, indicating that the neutralizing activity was **L1** specific. Disruption of the partially purified **L1** particles, by boiling in 1% SDS, abolished the ability of the preparation to induce neutralizing antibodies (Table 1). The demonstration that **L1** can self-assemble into virion-like particles that elicit neutralizing antisera titers at least three orders of magnitude higher than previous in vitro-produced antigens suggests the recombinant **L1** capsid proteins has the potential to induce effective long term protection against naturally transmitted **papillomavirus**. In view of these results, it appears that the **L1** particles assembled in insect

cells mimic infectious virus in the presentation of conformationally dependent immunodominant epitopes. These results also establish. . . L2 is not required for the generation of high titer neutralizing antibodies. The reported weak neutralizing immunogenicity of bacterially derived **L1** may occur because it does not assume an appropriate conformation or has not assembled into virion like structures. Also, multiple electrophoretic variants of **L1** have been detected in virions (Larsen, P., et al., 1987). Some of these modified species, which are probably absent in the bacterially derived **L1**, may facilitate the generation of neutralizing antibodies.

DETDESC:

DETD(33)

The ability of recombinant **L1** (or L2) **papillomavirus** capsid proteins such as those disclosed herein to induce high titer neutralizing antiserum makes them suitable for use as vaccines. . . that could benefit from immunization are bovine herds, which are susceptible to papilloma warts; all humans for non-genital types of **HPV** infection; and sexually active humans for genital **HPV** types of infection.

DETDESC:

DETD(34)

Therapeutic vaccination can be useful for productive **papillomavirus** lesions, which usually express **L1** (and L2) capsid proteins. Such lesions are most likely to occur in benign infections, such as warts or laryngeal papillomatosis. Laryngeal papillomatosis in newborns is usually contracted by the infant during passage through the birth canal where infectious **papillomavirus** is present in vaginal secretions. Therapeutic vaccination of infected pregnant women against the **papillomavirus** can induce neutralizing IgG antibody capable of passing through the placental barrier and into the circulation of the fetus to provide prophylactic passive immunity in the infant against this type of **papillomavirus** infection. Additional infant-protecting mechanisms are provided by maternal IgA which is secreted into the vaginal fluid and into breast milk. Jarrett (1991) demonstrates some therapeutic efficacy for L2 in treating BPV-induced warts. Malignant tumors typically do not express **L1** or L2, and the efficacy of vaccination with recombinant **L1** or L2 in conditions such as cervical cancer, is uncertain.

DETDESC:

DETD(35)

Protective immunity against both benign and malignant **papillomavirus** disease can be induced by administering an effective amount of recombinant **L1** capsid protein to an individual at risk for **papillomavirus** infection. A vaccine comprising the capsid protein can be directly administered, either parenterally or locally, according to conventional immunization protocols. In an alternative embodiment, the conformational coding sequence of **L1** can be cloned into a transfer vector, for example, a semliki forest virus vector (which produces a mild transient infection),. . .

DETDESC:

DETD(37)

Published serologic studies of human immune response to **papillomavirus** virion proteins have principally utilized bacterially derived **L1** and L2 capsid proteins, and the results have not correlated well with other measures of **HPV** infection (Jenison, S., et al., 1990). BPV **papillomavirus** immunity studies described above indicate that **papillomavirus** virion proteins extracted from bacteria do not present the conformationally dependent epitopes that appear to be type-specific and recognized by most neutralizing antibodies. Compared with such assays that primarily recognize linear epitopes, a serological test using self-assembled **L1** particles is likely to be a more accurate measure of the extent of anti-**HPV** virion immunity in the human population. The recombinant **L1** capsid proteins disclosed herein, presenting conformational epitopes, can therefore be used as highly specific diagnostic reagents to detect immunity conferring. . .

DETDESC:

DETD(38)

The recombinant **L1** or **L1**/L2 capsid proteins disclosed herein can also be used to measure cellular immunity to **papillomavirus** by means of in vivo or in vitro assays, for example, antigen-induced T-cell proliferative responses as described by Bradley, L.,. . . 1980, and particularly cellular responses to viral antigens, as described in U.S. Pat. No. 5,081,029 to Starling. Cellular immunity to **papillomavirus** can also be determined by the classical in vivo delayed hypersensitivity skin test as described by Stites, D., 1980; or in a preferred method, according to Hopfl, R., et al., 1991, by the intradermal injection of recombinant **HPV** **L1** fusion proteins.

DETDESC:

DETD(39)

The . . . also be used as immunogens to raise polyclonal or monoclonal antibodies, according to methods well known in the art. These **papillomavirus**-specific antibodies, particularly in combination with labelled second antibodies, specific for a class or species of antibodies, can be used diagnostically. . .

DETDESC:

DETD(43)

Full length **L1**, or **L1** and L2 open reading frames (ORF) were amplified by PCR using the cloned prototypes of BPV1 DNA (Chen, E., et. . .

DETDESC:

DETD(44)
BPV1-**L1** primer sequence (Sequence ID No. 3):

DETDESC:

DETD(47)
HPV16-**L1** primer sequence (Sequence ID No. 5):

DETDESC:

DETD(50)
L1 coding sequences begin at the 1st methionine codon (bold) for BPV1 and the 2nd methionine for HPV16. BPV1-**L1** was cloned as a 5'-EcoRI to 3'-KpnI fragment and HPV16-**L1** as a 5'-BglII to 3'-BglII fragment into the multiple cloning site downstream of the polyhedrin promoter of the AcMNPV based baculovirus transfer vector pEV mod (Wang, X., et al. 1991) and verified by sequencing through the AcMNPV/**L1** junction. A quantity of 2 .mu.g of CsCl-purified recombinant plasmid was cotransfected with 1 .mu.g wild type AcMNPV DNA (Invitrogen,. . .

DETDESC:

DETD(52)

Expression of **L1** Proteins or **L1**/L2 Proteins in Insect Cells

DETDESC:

DETD(53)

Sf-9 . . . were either mock infected (mock) or infected at a multiplicity of infection of 10 with either wt AcMNPV (wt) or AcBPV-**L1** (B-**L1**), AcHPV16-**L1** (16-**L1**), or AcHPV16-**L1** (16-**L1**) and AcHPV16-L2 (16-L2) recombinant virus. After 72 hours, cells were lysed by boiling in Laemmli buffer and the lysates subjected. . .

DETDESC:

DETD(56)

Rabbits . . . (3.times.10.sup.7 cells) prepared by one freeze/thaw cycle and 20.times. dounce homogenization (rabbit #1,2, and 8) or with 200 .mu.g of **L1** protein partially purified by differential centrifugation and 35% ammonium sulfate precipitation (#3,4,6, and 7), in complete Freund's adjuvant, and then. . .

DETDESC:

DETD(59)

500 ml of Sf-9 cells (2.times.10.sup.6 /ml) were infected with AcBPV-**L1** (FIG. 2A) or AcHPV16-**L1** (FIG. 2C) or or AcHPV16-**L1**/L2 (16-**L1**/L2) recombinant baculoviruses. After 72 hr, the harvested cells were sonicated in PBS for 60 sec. After low speed clarification, the. . . the bottom and analyzed by SDS-PAGE. Immunoreactive fractions were dialyzed against PBS, concentrated by Centricon 30 (Millipore) ultrafiltration, and (for HPV16-**L1**) pelleted by centrifugation for 10 min at 30 psi in a A-100 rotor in an airfuge (Beckman). BPV1 virions (FIG.. . .

DETDESC:

DETD(62)

Serial . . . results are shown in FIG. 3 and are discussed below. The antisera and dilutions used are indicated below the plates. Anti-AcBPV-**L1** was obtained from rabbit #1 and anti-wt AcMNPV from rabbit #8 (Table 1). The normal rabbit serum negative control is. . .

DETDESC:

DETD(65)

Assays . . . #1, 2, and 8 were inoculated with crude whole cell Sf-9 lysates, and rabbits #3,4,6, and 7 with partially purified **L1** protein (Table 1). Rabbits #6 and 7 were immunized with **L1** protein preparations that had been denatured by boiling in 1% SDS. At least two bleeds, taken 3-6 weeks after the. . .

DETDESC:

DETD(66)

TABLE 1

	rabbit	serum neutralization titer against BPV1*
AcBPV-**L1**	1	11,000
"	2	97,000
"	3	290,000
"	4	97,000
BPV1-virions	5	290,000
AcBPV-**L1**/SDS	6	<2
"	7	<2
wt AcMNPV	8	<20

*reciprocal of dilution that caused 50% focus reduction. . .

DETDESC:

DETD(80)
Ghim, S., et al. HPV1-**L1** protein expressed in cos cells displays conformational epitopes found on intact virions. Virology 190:548-552 (1992).

DETDESC:

DETD(81)
Hagensee, M., et al. Self-assembly of human **papillomavirus** type 1 capsids by expression of the **L1** protein alone or by coexpression of the **L1** and L2 capsid proteins. J. of Virology 67(1):315-322.

DETDESC:

DETD(82)
Hopfl, R., et al. Skin test for **HPV** type 16 proteins in cervical intraepithelial neoplasia. Lancet 337:373 (1991).

DETDESC:

DETD(86)
Jenson, A., et al. Identification of linear epitopes BPV-1 **L1** protein recognized by sera of infected or immunized animals. Pathobiology 59:396 (1991)

DETDESC:

DETD(89)
Kirnbauer, R., et al. **Papillomavirus** **L1** major capsid protein self-assembles into virus-like particles that are highly immunogenic. Proc. Natl. Acad. Sci. USA 89:12180-12184 (1992).

DETDESC:

DETD(92)
Lin, Y- L., et al. Effective vaccination against papilloma development by immunization with **L1** or L2 structural protein of cottontail rabbit papillovirus. Virology 187:612 (1992).

DETDESC:

DETD(93)
McLean, C., et al. Production and characterization of a monoclonal antibody to human **papillomavirus** type 16 using recombinant vaccinia virus. J. Clin. Pathol 43:488 (1990).

DETDESC:

DETD(98)
Seedorf, et al. Human **papillomavirus** type 16 DNA seqeunce. Virology 145:181-185 (1985)

DETDESC:

DETD(103)
Zhou, J., et al. Expression of vaccinia recombinant **HPV** 16 **L1** and L2 ORF proteins in epithelial cells is sufficient for assembly of **HPV** virion-like particles. J. Virology 185:251 (1991).

DETDESC:

DETD(105)
. . .
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vi) ORIGINAL SOURCE:
(A) ORGANISM: Human **papillomavirus**
(B) STRAIN: HPV16
(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1517
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
ATGTCTCTTTGGCTGCCTAGTGAGGCCACTGTCTACTTGCCTCCTGTC48

MetSerLeuT rpLeuProSerGluAlaThrValTyrLeuProProVal. . .
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vi) ORIGINAL SOURCE:
(A) ORGANISM: Bovine **papillomavirus**
(vii) IMMEDIATE SOURCE:
(B) CLONE: BPV1 N
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:
CCGCTGAATTCAATATGGCGTTGTGGCAACAAGGCCAGAAGCTGTAT47
(2) INFORMATION FOR SEQ ID. . .

CLAIMS:

CLMS(1)

What is claimed is:

1. A genetic construct comprising a **papillomavirus** **L1** gene wherein said construct directs recombinant expression in a transformed eukaryotic host cell of at least one **papillomavirus** **L1** epitope by self-assembly of **papillomavirus** capsids comprising a **L1** polypeptide, wherein said **L1** polypeptide is characterized as having the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:2.

CLAIMS:

CLMS(2)

2. The construct of claim 1, wherein said **L1** polypeptide is characterized as being encoded by the nucleotide sequence of SEQ ID NO:2.

CLAIMS:

CLMS(3)

3. The construct of claim 1, wherein said **papillomavirus** capsids further comprise a L2 polypeptide, and wherein recombinant expression of said L2 polypeptide is directed either by said construct further comprising a **papillomavirus** L2 gene or a different genetic construct comprising a **papillomavirus** L2 gene.

CLAIMS:

CLMS(4)

4. The construct of claim 3 further comprising said **papillomavirus** L2 gene.

CLAIMS:

CLMS(13)

13. A method for producing at least one **papillomavirus** **L1** epitope, comprising the step of:
permitting a genetic construct, comprising a **papillomavirus** **L1**

gene, to direct recombinant expression in a transformed eukaryotic host cell of at least one **papillomavirus** **L1** epitope by self-assembly of **papillomavirus** capsids comprising a **L1** polypeptide, wherein said **L1** polypeptide is characterized as having the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:2.

CLAIMS:

CLMS(14)

14. The method of claim 13, wherein said **L1** polypeptide is characterized as being encoded by the nucleotide sequence of SEQ ID NO:2.

CLAIMS:

CLMS(15)

15. The method of claim 13, wherein said **papillomavirus** capsids further comprise a L2 polypeptide, and wherein recombinant expression of said L2 polypeptide is directed either by said construct further comprising a **papillomavirus** L2 gene or a different genetic construct comprising a **papillomavirus** L2 gene.

CLAIMS:

CLMS(16)

16. The method of claim 15, wherein said construct further comprises said **papillomavirus** L2 gene.

CLAIMS:

CLMS(23)

23. The method of claim 13, further comprising isolating said **papillomavirus** capsids from said transformed host cell.

```
=> s HPV
L4          131 HPV
=> s human papillomavirus
         124125 HUMAN
             99 PAPILLOMAVIRUS
L5           45 HUMAN PAPILLOMAVIRUS
                   (HUMAN(W)PAPILLOMAVIRUS)
=> s l4 or l5
L6          138 L4 OR L5
=> d his
     (FILE 'USPAT' ENTERED AT 14:33:00 ON 12 SEP 95)
L1        23082 S "L1"
L2          190 S HPV OR PAPILLOMAVIRUS
L3           20 S L1 AND L2
L4          131 S HPV
L5           45 S HUMAN PAPILLOMAVIRUS
L6          138 S L4 OR L5
=> s l6 and l1
L7           20 L6 AND L1
=> s l6(5a)l1
L8           10 L6(5A)L1
=> d l8 1-10 kwic
```

US PAT NO: 5,447,839 [IMAGE AVAILABLE] L8: 1 of 10

DETDESC:

DETD(14)

The . . . or more regions of the HPV genome. The methods and compositions described herein are particularly suited for amplifying the following **HPV** regions: **L1**/URR, **L1**, E6, E6/E7, E7 through E1, E6 through E 1, and E1. It will be clear to one of ordinary skill. . .

DETDESC:

DETD(22)

In . . . embodiment, the L1/E6 consensus primer combinations of the invention are designed to amplify a sequence of DNA from any genital **HPV**. The amplified sequence extends from **L1** across the URR and into E6 and thus contains portions of the L1 and E6 regions with the URR region. . .

DETDESC:

DETD(25)

Once . . . PCR, the method of the invention requires the determination of whether amplification has occurred. If amplification has occurred with the **L1**/E6 primers, **HPV** sequences are present in the sample. In one aspect of the invention, a consensus probe is used to determine if amplification has occurred. Alternatively, amplification of **HPV** DNA using the **L1**/E6 consensus primers FS10, JS15, and JS16 can be detected using the L1/E6 consensus primer FS17 or MY01.

DETDESC:

DETD(27)

TABLE 2

HPV Typing Probes For Use with **L1**/E6 Consensus Primers

Specificity	Sequence	Size	Designation
HPV6	5'CCAAACAGTAAGAGC	(15-mer)	FS18
HPV11	5'GGCTGTAGAGGGCTTAGAC	(19-mer)	FS19
HPV16	5'GGTTGAAGCTACAAAATGGGCC. . .		

DETDESC:

DETD(33)

As . . . for determining if amplification has occurred. According to

Example 1, a generic probe was synthesized from the 450 base pair **L1** PCR fragments of **HPV**-16, **HPV**-18, and the highly divergent isolates PAP88 and PAP238B. The generic probe described in Example 1 comprises segments approximately 400 base. . .
SYSTEM LIMITS EXCEEDED - DISPLAY ENDED
=> d l8 2-10 kwic

US PAT NO: 5,437,951 [IMAGE AVAILABLE] L8: 2 of 10

ABSTRACT:
Recombinant . . . The capsomer structures and viral capsids, consisting of the capsid proteins that are expression products of a bovine, monkey or **human** **papillomavirus** **L1** conformational coding sequence proteins, can be prepared as vaccines to induce a high-titer neutralizing antibody response in vertebrate animals. The. . .

SUMMARY:

BSUM(9)

In . . . al., 1992), neither of which has the structural features of native virions, had low titers, and the use of recombinant **HPV** **L1** fusion peptides expressed in E. coli to detect cellular immune reactivity has had only limited success (Hopfl, R. et al.,. . .

SUMMARY:

BSUM(10)

There . . . isolated attempts to produce papillomavirus capsids in vitro. Zhou, J. et al. (1991) and (1992) produced virus-like particles by cloning **HPV** **L1** and L2 genes, and **HPV** **L1** and L2 genes in combination with HPV E3/E4 genes into a vaccinia virus vector and infecting CV-1 mammalian cells with. . . and L2 proteins showed small (40 nm) virus-like particles in the nucleus that appeared to be incompletely assembled arrays of **HPV** capsomers. Expressing **L1** protein alone, or L2 protein alone, was expressed did not produce virus-like particles; cells doubly infected with singly recombinant vaccinia. . .

SUMMARY:

BSUM(21)

The . . . having immunogenic conformational epitopes capable of inducing neutralizing antibodies against native papillomavirus. The capsid proteins can be bovine, monkey or **human** **papillomavirus** **L1** proteins. In a preferred embodiment, the papillomavirus L1 capsid protein is the expression product of a wild type HPV16 L1. . .

SUMMARY:

BSUM(26)

Also . . . of said vertebrate, whereby an effective, neutralizing, immune response to papillomavirus is induced. In a preferred embodiment, the conformational papillomavirus **L1** coding sequence is derived from

human **papillomavirus** HPV16. In a particularly preferred embodiment, the human papillomavirus HPV16 is a wild type papillomavirus.

DETDESC:

DETD(6)

The . . . particles with an efficiency similar to that seen with BPV L1 or BPV L1/L2. Compared with the self-assembly seen when **L1** from the prototype **HPV** genome is used with L2, **L1** from a wild-type genome self-assembles at least 100 times more efficiently.

DETDESC:

DETD(20)

The . . . neutralizing antibodies and may therefore be suitable for vaccine production. Particles comprising L1 capsid protein expressed by a wild type **HPV** genome, either as **L1** alone or L1/L2 together, are particularly preferred.

DETDESC:

DETD(22)

According . . . baculovirus system is used. The gene to be cloned, substantially all of the coding sequence for bovine papillomavirus (BPV1) or **human** **papillomavirus** (HPV16) **L1** capsid protein, or **human** **papillomavirus** HPV16 **L1** and L2, is inserted into a baculovirus transfer vector containing flanking baculovirus sequences to form a gene construct, and the. . .

DETDESC:

DETD(28)

To determine if the ability to self-assemble in insect cells is a general feature of papillomavirus L1, we also expressed the **L1** of HPV16, the **HPV** type most often detected in human genital cancers, via an analogous recombinant baculovirus. A protein of the expected 58 kd. . .

DETDESC:

DETD(38)

The . . . D., 1980; or in a preferred method, according to Hopfl, R., et al., 1991, by the intradermal injection of recombinant **HPV** **L1** fusion proteins.

DETDESC:

DETD(103)
Zhou, J., et al. Expression of vaccinia recombinant **HPV** 16 **L1** and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. J. Virology 185:251 (1991).

US PAT NO: 5,334,515 [IMAGE AVAILABLE] L8: 3 of 10

DETDESC:

DETD(94)

Preparation of RNA Analyte: A DNA segment from the **L1** region of Human Papilloma Virus (**HPV**) type 16 was cloned into plasmid vector pT7-13 (BRL) behind a T7 RNA Polymerase promoter. In vitro transcription was performed. . .

US PAT NO: 5,283,171 [IMAGE AVAILABLE] L8: 4 of 10

SUMMARY:

BSUM(21)

For instance, the L1/E6 consensus primer combinations of the invention are designed to amplify a sequence of DNA from any genital **HPV**. The amplified sequence extends from **L1** across the URR and into E6 and thus contains portions of the L1 and E6 regions with the URR region. . .

SUMMARY:

BSUM(25)

Once . . . PCR, the method of the invention requires the determination of whether amplification has occurred. If amplification has occurred with the **L1**/E6 primers, **HPV** sequences are present in the sample. The use of an internal amplification control to assure the competency of a sample. . . probe must be a consensus probe so that amplified DNA from any HPV can be detected. For instance, amplification of **HPV** DNA using the **L1**/E6 consensus primers FS10, JS15, and JS16 can be detected using the L1/E6 consensus primer FS17 or MY01. Alternatively, the determination. . .

SUMMARY:

BSUM(29)

TABLE 2

HPV Typing Probes For Use with **L1**/L6 Consensus Primers	Sequence	Size	Designation	Specificity
HPV6	5'CCAAACAGTAAGAGC	(15-mer)	FS18	
HPV11	5'GGCTGTAGAGGGCTTAGAC	(19-mer)	FS19	
HPV16	5'GGTTGAAGCTACAAAATGGGCC. . .			

SYSTEM LIMITS EXCEEDED - DISPLAY ENDED
YOU HAVE RECEIVED THIS ERROR MESSAGE 2 CONSECUTIVE TIMES
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KWIC display format is used and when a character string search is attempted using the Display Browse command.

If you had been attempting to use the KWIC format, use the HIT format or any other display format instead of KWIC. (Enter HELP FORMAT for a list of available display formats). If you had been attempting a character string search in Display Browse, end Display Browse and search for the requested term(s) using the Search command. To display your search results, use HIT rather than KWIC.
IF YOU REQUIRE FURTHER HELP, PLEASE CONTACT YOUR LOCAL HELP DESK
=> d l8 4-10 kwic

US PAT NO: 5,283,171 [IMAGE AVAILABLE] L8: 4 of 10

SUMMARY:

BSUM(21)

For instance, the L1/E6 consensus primer combinations of the invention are designed to amplify a sequence of DNA from any genital **HPV**. The amplified sequence extends from **L1** across the URR and into E6 and thus contains portions of the L1 and E6 regions with the URR region. . .

SUMMARY:

BSUM(25)

Once . . . PCR, the method of the invention requires the determination of whether amplification has occurred. If amplification has occurred with the **L1**/E6 primers, **HPV** sequences are present in the sample. The use of an internal amplification control to assure the competency of a sample. . . probe must be a consensus probe so that amplified DNA from any HPV can be detected. For instance, amplification of **HPV** DNA using the **L1**/E6 consensus primers FS10, JS15, and JS16 can be detected using the L1/E6 consensus primer FS17 or MY01. Alternatively, the determination. . .

SUMMARY:

BSUM(29)

TABLE 2

HPV Typing Probes For Use with **L1**/L6 Consensus Primers

Specificity	Sequence	Size	Designation
HPV6	5'CCAAACAGTAAGAGC	(15-mer)	FS18
HPV11	5'GGCTGTAGAGGGCTTAGAC	(19-mer)	FS19
HPV16	5'GGTTGAAGCTACAAAATGGGCC. . .		

SYSTEM LIMITS EXCEEDED - DISPLAY ENDED
=> d l8 5-10 kwic

US PAT NO: 5,194,370 [IMAGE AVAILABLE] L8: 5 of 10

DETDESC:

DETD(163)

The 5'-end of 668 bp target RNA was an in vitro transcript of **human** **papillomavirus** type 16 open reading frame **L1** (Seedorf K. et al. (1985) Virol. 145:181-185). The reverse complement of the 85-mer DNA target was totally contained within the. . .

US PAT NO: 5,182,377 [IMAGE AVAILABLE] L8: 6 of 10

DETDESC:

DETD(15)

For instances, the L1/E6 consensus primer combinations of the invention are designed to amplify a sequence of DNA from any genital **HPV**. The amplified sequence extends from **L1** across the URR and into E6 and thus contains portions of the L1 and E6 regions with the URR region. . .

DETDESC:

DETD(19)

Once . . . PCR, the method of the invention requires the determination of whether amplification has occurred. If amplification has occurred with the **L1**/E6 primers, **HPV** sequences are present in the sample. The use of an internal amplification control to assure the competency of a sample. . . probe must be a consensus probe so that amplified DNA from any HPV can be detected. For instance, amplification of **HPV** DNA using the **L1**/E6 consensus primers FS10, JS15, and JS16 can be detected using the L1/E6 consensus primer FS17 or MY01. Alternatively, the determination. . .

DETDESC:

DETD(23)

TABLE 2

HPV Typing Probes For Use with **L1**/E6 Consensus Primers Specificity	Sequence	Size	Designation
HPV6	5'CCAAACAGTAAGAGC	(15-mer)	FS18
HPV11	5'GGCTGTAGAGGGCTTAGAC	(19-mer)	FS19
HPV16	5'GGTTGAAGCTACAAAATGGGCC. . .		

DETDESC:

DETD(31)

The DNA Sequence of the **L1** Amplified Regions of **HPV** Isolates 36A, 36B, 88, 238A, and 238B

Isolate 36A
1 GCMCAGGGWC
ATAAYAATGG
TATATGTTGG
CACAATCAAT
TGTTTTTAAC. . .

DETDESC:

DETD(36)

TABLE 5

HPV Typing Probes For Use with **L1** Consensus Primers

Probe	Specificity	Sequence	Genome Position
MY12	HPV6	5'CATCCGTAACTACATCTTCCA	6813-6833
MY13	HPV11	5'TCTGTGTCTAAATCTGCTACA	6800-6820
MY14. . .			

CLAIMS:

CLMS(1)

We claim:

1. AN **HPV** **L1** consensus probe selected from the group consisting of probes MY66, MY55, MY39, MY56, and MY57.

US PAT NO: 5,169,766 [IMAGE AVAILABLE] L8: 7 of 10

DETDESC:

DETD(44)

A DNA segment from the **L1** region of Human Papilloma Virus (**HPV**) type 16 wascloned into plasmid vector pT71 (USB) behind a T7 RNA Polymerase promoter. In vitro transcription was performed using. . .

US PAT NO: 5,045,447 [IMAGE AVAILABLE] L8: 8 of 10

DETDESC:

DETD(3)

(1) Preparation of **HPV**-16 **L1**/.beta.-galactosidase fusion protein (the immunogen)

DETDESC:

DETD(4)

A . . . Seedorf et al 1985, Virology 145, 181, incorporated herein by reference). A portion (amino acid 211 to C-terminus) of the **HPV**-16 **L1** open reading frame was cloned as a Bam H1/Sph1 fragment (bases 6153-7464) from a genomic clone of HPV-16 DN and. . . 3, 1429, incorporated herein by reference), to yield a fused open reading frame of .beta.-galactosidase and the C-terminal portion of **HPV**-16 **L1**. The resulting plasmid pHX2 was transfected into E.coli POP 2136 and heat induction resulted in the production of a .beta.-gal. . .

DETDESC:

DETD(5)

(2) Preparation of a recombinant vaccinia virus expressing the full length **HPV**-16 **L1** protein (the screening target)

DETDESC:

DETD(6)

The **HPV**-16 **L1** open reading frame was introduced into the vector pUC18 in a Kpn1--Sph1 fragment (bases 5377-7464) derived from an HPV-16 genomic. . .

DETDESC:

DETD(7)

The resulting plasmid, pRKL1, contains the entire **HPV**-16 **L1** gene under the control of the vaccinia late promoter. See FIG. 4. pRKL1 was transfected into CV-1 cells infected with. . . identified by hybridization with a HPV-16 DNA probe and further characterised by restriction enzyme digestion. A recombinant virus containing the **HPV**-16 **L1** gene inserted in the correct orientation was identified, and named vL1RK.

DETDESC:

DETD(14)

(3) Production of, monoclonal antibodies to **HPV**-16 **L1**

DETDESC:

DETD(15)

Mice . . . cells and the fusion products were distributed among 48.times. 1.5 cm diameter tissue culture wells. Culture supernatants were screened for **HPV**-16 **L1**-specific antibody by immunofluorescence assay using as a target BHK-21 fibroblasts infected with vLIRK as

follows.

DETDESC:

DETD(17)

The . . . from lysates of cells infected with wild-type vaccinia virus. This apparent Mr was consistent with the predicted Mr of the **HPV**-16 **L1** protein of about 53,000. The antibody was also found to give strong nuclear staining (using immunofluorescence and/or immunoperoxidase staining) of. . .

DETDESC:

DETD(23)

A . . . Luzio, supra) to generate a fused .beta.-galactosidase-E7 coding sequence pExE7. See FIG. 5. The expressed product was induced and the **HPV**-16 **L1** fusion protein purified (See Browne et al, supra).

DETDESC:

DETD(27)

The .beta.-galactosidase-E7 fusion, protein (prepared in (a) above) was used to immunize mice as described for the **HPV**-16 **L1** fusion protein, followed by the other procedures set forth in Part (3) above to provide CAMVIR-2 and -3. See the. . .

CLAIMS:

CLMS(3)

3. The improved method of claim 1, wherein the epitope is comprised in the **HPV**-16 **L1** protein or **HPV**-16 E7 protein.

US PAT NO: 4,886,741 [IMAGE AVAILABLE] L8: 9 of 10

SUMMARY:

BSUM(37)

In the alternative, patent application W086/05816 discloses both a genus specific and type specific region for the **HPV** genome located within the **L1** gene encoding the major component of the viral coat.

US PAT NO: 4,551,270 [IMAGE AVAILABLE] L8: 10 of 10

DETDESC:

DETD(5)

However, preferably, the invention relates to DNA fragments having common nucleotide sequences with the abovesaid **L1** region of **HPV** 1a.
=> d l8 8

8. 5,045,447, Sep. 3, 1991, Method of producing antibodies to HPV;

Anthony C. Minson, 435/5; 422/61; 435/7.92; 436/548; 935/110 [IMAGE AVAILABLE]
=>

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=> file medline

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'AB' IS NOT A VALID FIELD CODE
             0 ("L1")/AB
          4899 ("L1")/BI
L1        4899 ("L1")/AB,BI

=> s (human papillomavirus)/ab,bi or (HPV)/ab,bi

'AB' IS NOT A VALID FIELD CODE
             0 (HUMAN PAPILLOMAVIRUS)/AB
       5439025 HUMAN/BI
          6686 PAPILLOMAVIRUS/BI
          3712 (HUMAN PAPILLOMAVIRUS)/BI
                 ((HUMAN(W)PAPILLOMAVIRUS)/BI)
             0 (HPV)/AB
          4056 (HPV)/BI
L2        5129 (HUMAN PAPILLOMAVIRUS)/AB,BI OR (HPV)/AB,BI

=> s l1 and l2

L3         223 L1 AND L2

=> s recombinant/ab,bi

'AB' IS NOT A VALID FIELD CODE
             0 RECOMBINANT/AB
         82383 RECOMBINANT/BI
L4       82383 RECOMBINANT/AB,BI

=> s l3 and l4
```

L5 56 L3 AND L4

=> d l5 1-56

L5 ANSWER 1 OF 56 MEDLINE
AN 95340788 MEDLINE
TI Detection of antibodies against ***human*** ***papillomavirus*** (***HPV***) type 16 virions by enzyme-linked immunosorbent assay using ***recombinant*** ***HPV*** 16 ***L1*** capsids produced by ***recombinant*** baculovirus.
AU Le Cann P; Touze A; Enogat N; Leboulleux D; Mougin C; Legrand M C; Calvet C; Afoutou J M; Coursaget P
CS Service des Maladies Infectieuses, Hopital de Fann, Dakar, Senegal.
SO J Clin Microbiol, (1995 May) 33 (5) 1380-2.
Journal code: HSH. ISSN: 0095-1137.
CY United States
DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9510

L5 ANSWER 2 OF 56 MEDLINE
AN 95251779 MEDLINE
TI The expressed ***L1*** proteins of ***HPV*** -1, ***HPV*** -6, and ***HPV*** -11 display type-specific epitopes with native conformation and reactivity with neutralizing and nonneutralizing antibodies.
AU Hines J F; Ghim S J; Christensen N D; Kreider J W; Barnes W A; Schlegel R; Jenson A B
CS Department of Pathology, Georgetown University Medical Center, Washington, DC 20007-2197, USA.
NC R01CA47622 (NCI)
R01CA57994 (NCI)
R01CA50812 (NCI)
SO Pathobiology, (1994) 62 (4) 165-71.
Journal code: AF6. ISSN: 1015-2008.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9508

L5 ANSWER 3 OF 56 MEDLINE
AN 95133149 MEDLINE
TI Immunization of mice with ***HPV*** vaccinia virus recombinants generates serum IgG, IgM, and mucosal IgA antibodies.
AU Hagensee M E; Carter J J; Wipf G C; Galloway D A
CS Fred Hutchinson Cancer Research Center, Seattle, Washington 98104-2029.
NC CA42792 (NCI)
AI29363 (NIAID)
SO Virology, (1995 Jan 10) 206 (1) 174-82.
Journal code: XEA. ISSN: 0042-6822.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9504

L5 ANSWER 4 OF 56 MEDLINE
AN 95133143 MEDLINE
TI Synthesis and assembly of virus-like particles of human papillomaviruses type 6 and type 16 in fission yeast Schizosaccharomyces pombe.
AU Sasagawa T; Pushko P; Steers G; Gschmeissner S E; Hajibagheri M A; Finch J; Crawford L; Tommasino M
CS Imperial Cancer Research Fund Tumour Virus Group, Department of Pathology, Cambridge, United Kingdom.
SO Virology, (1995 Jan 10) 206 (1) 126-35.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9504

L5 ANSWER 5 OF 56 MEDLINE
AN 95121629 MEDLINE
TI Expression of ***human*** ***papillomavirus*** type 16 (***HPV*** -16) major (***L1***) and minor (L2) capsid proteins in insect cells as polyhistidine fusion proteins.
AU Cason J; Kambo P K; Manse C; Jewers R J; Best J M
CS Richard Dimbleby Laboratory of Cancer Virology, London.
SO Biochem Soc Trans, (1994 Aug) 22 (3) 336S.
Journal code: E48. ISSN: 0300-5127.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9504

L5 ANSWER 6 OF 56 MEDLINE
AN 95121628 MEDLINE
TI Detection of protein aggregates, but not virus-like particles, when the major (***L1***) coat protein of a wild-type ***human*** ***papillomavirus*** type 16 (***HPV*** -16) is expressed in insect cells.
AU Cason J; Kambo P K; Jewers R J; Best J M
CS Laboratory of Cancer Virology, Rayne Institute, St Thomas' Hospital, London, U.K.
SO Biochem Soc Trans, (1994 Aug) 22 (3) 335S.
Journal code: E48. ISSN: 0300-5127.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9504

L5 ANSWER 7 OF 56 MEDLINE
AN 95088581 MEDLINE
TI Analysis of type-restricted and cross-reactive epitopes on virus-like particles of ***human*** ***papillomavirus***

type 33 and in infected tissues using monoclonal antibodies to the major capsid protein.
AU Sapp M; Kraus U; Volpers C; Snijders P J; Walboomers J M; Streeck R E
CS Institut fur Medizinische Mikrobiologie, Johannes-Gutenberg-Universitat Mainz, Germany.
SO J Gen Virol, (1994 Dec) 75 (Pt 12) 3375-83.
Journal code: I9B. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9503

L5 ANSWER 8 OF 56 MEDLINE
AN 95053930 MEDLINE
TI Brief report: antibody response to E6, E7, and ***L1*** proteins of ***human*** ***papillomavirus*** 16 in an Italian population.
AU Di Lonardo A; Campo M S; Venuti A; Marcante M L
CS Laboratory of Virology, CRS-Regina Elena Institute for Cancer Research, Rome, Italy.
SO J Med Virol, (1994 Aug) 43 (4) 357-61.
Journal code: I9N. ISSN: 0146-6615.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9502

L5 ANSWER 9 OF 56 MEDLINE
AN 95047752 MEDLINE
TI Role of conformational epitopes expressed by ***human*** ***papillomavirus*** major capsid proteins in the serologic detection of infection and prophylactic vaccination [see comments].
CM Comment in: Gynecol Oncol 1994 Oct;55(1):10-2
AU Hines J F; Ghim S J; Christensen N D; Kreider J W; Barnes W A; Schlegel R; Jenson A B
CS Department of Obstetrics and Gynecology, Georgetown University Medical Center, Washington, DC 20007.
NC RO1CA47622 (NCI)
R01CA57994 (NCI)
R01CA50812 (NCI)
SO Gynecol Oncol, (1994 Oct) 55 (1) 13-20.
Journal code: FXC. ISSN: 0090-8258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9502

L5 ANSWER 10 OF 56 MEDLINE
AN 95018603 MEDLINE
TI Low-affinity E2-binding site mediates downmodulation of E2 transactivation of the ***human*** ***papillomavirus*** type 8 late promoter.
AU Stubenrauch F; Pfister H
CS Institut fur Klinische und Molekulare Virologie, Universitat

Erlangen-Nurnberg, Germany.
SO J Virol, (1994 Nov) 68 (11) 6959-66.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9501

L5 ANSWER 11 OF 56 MEDLINE
AN 94358748 MEDLINE
TI Serological differentiation of ***human*** ***papillomavirus*** types 11, 16 and 18 using ***recombinant*** virus-like particles.
AU Rose R C; Bonnez W; Da Rin C; McCance D J; Reichman R C
CS Department of Medicine, University of Rochester School of Medicine and Dentistry, New York 14642.
NC AI-82509 (NIAID)
SO J Gen Virol, (1994 Sep) 75 (Pt 9) 2445-9.
Journal code: I9B. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9412

L5 ANSWER 12 OF 56 MEDLINE
AN 94267912 MEDLINE
TI Three-dimensional structure of vaccinia virus-produced ***human*** ***papillomavirus*** type 1 capsids.
AU Hagensee M E; Olson N H; Baker T S; Galloway D A
CS Program in Cancer Biology, Fred Hutchinson Cancer Research Center, Seattle, Washington 98104-2092.
NC AI07044 (NIAID)
CA42792 (NCI)
GM33050 (NIGMS)
SO J Virol, (1994 Jul) 68 (7) 4503-5.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9409

L5 ANSWER 13 OF 56 MEDLINE
AN 94259262 MEDLINE
TI Self-assembly of ***human*** ***papillomavirus*** type 16 capsids by expression of the ***L1*** protein in insect cells.
AU Le Cann P; Coursaget P; Iochmann S; Touze A
CS Institut de Virologie de Tours, Faculte de Pharmacie, France.
SO FEMS Microbiol Lett, (1994 Apr 15) 117 (3) 269-74.
Journal code: FML. ISSN: 0378-1097.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9409

L5 ANSWER 14 OF 56 MEDLINE
AN 94233775 MEDLINE
TI Colocalization of ***human*** ***papillomavirus*** type 11 E1[symbol: see text]E4 and ***L1*** proteins in human foreskin implants grown in athymic mice.
AU Brown D R; Fan L; Jones J; Bryan J
CS Department of Medicine, Indiana University School of Medicine, Indianapolis 46202.
SO Virology, (1994 May 15) 201 (1) 46-54.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9408

L5 ANSWER 15 OF 56 MEDLINE
AN 94233713 MEDLINE
TI Assembly of the major and the minor capsid protein of ***human*** ***papillomavirus*** type 33 into virus-like particles and tubular structures in insect cells.
AU Volpers C; Schirmacher P; Streeck R E; Sapp M
CS Institute fur Medizinische Mikrobiologie, Universitat Mainz, Germany.
SO Virology, (1994 May 1) 200 (2) 504-12.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9408

L5 ANSWER 16 OF 56 MEDLINE
AN 94180404 MEDLINE
TI A virus-like particle enzyme-linked immunosorbent assay detects serum antibodies in a majority of women infected with ***human*** ***papillomavirus*** type 16 [see comments].
CM Comment in: J Natl Cancer Inst 1994 Apr 6;86(7):474-5
AU Kirnbauer R; Hubbert N L; Wheeler C M; Becker T M; Lowy D R; Schiller J T
CS Laboratory of Cellular Oncology, National Cancer Institute, Bethesda, Md. 20892.
NC R0132917-03 (NCI)
CA48003
SO J Natl Cancer Inst, (1994 Apr 6) 86 (7) 494-9.
Journal code: J9J. ISSN: 0027-8874.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9406

L5 ANSWER 17 OF 56 MEDLINE
AN 94167862 MEDLINE
TI Use of ***HPV*** 1 capsids produced by ***recombinant*** vaccinia viruses in an ELISA to detect serum antibodies in people with foot warts.
AU Carter J J; Hagensee M B; Lee S K; McKnight B; Koutsky L A; Galloway

D A
CS Fred Hutchinson Cancer Research Center, Seattle, Washington 98104-2029.
NC CA42792 (NCI)
AI 29363 (NIAID)
SO Virology, (1994 Mar) 199 (2) 284-91.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9406

L5 ANSWER 18 OF 56 MEDLINE
AN 94157457 MEDLINE
TI Delayed-type hypersensitivity response to ***human*** ***papillomavirus*** type 16 E6 protein in a mouse model.
AU Chambers M A; Stacey S N; Arrand J R; Stanley M A
CS Department of Pathology, University of Cambridge, U.K.
SO J Gen Virol, (1994 Jan) 75 (Pt 1) 165-9.
Journal code: I9B. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
EM 9406

L5 ANSWER 19 OF 56 MEDLINE
AN 94149111 MEDLINE
TI ***Human*** ***papillomavirus*** type 16 E6, E7 and ***L1*** and type 18 E7 proteins produced by ***recombinant*** baculoviruses.
AU Park D S; Selvey L A; Kelsall S R; Frazer I H
CS Papillomavirus Research Unit, Lions Human Immunology Laboratories, University of Queensland, Princess Alexandra Hospital, Woolloongabba, Australia.
NC RO1-CA57789-01 (NCI)
SO J Virol Methods, (1993 Dec 31) 45 (3) 303-18.
Journal code: HQR. ISSN: 0166-0934.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9405

L5 ANSWER 20 OF 56 MEDLINE
AN 94118406 MEDLINE
TI Interaction of ***human*** ***papillomavirus*** (***HPV***) type 16 capsid proteins with ***HPV*** DNA requires an intact L2 N-terminal sequence.
AU Zhou J; Sun X Y; Louis K; Frazer I H
CS Papillomavirus Research Unit, University of Queensland, Princess Alexandra Hospital, Woolloongabba, Australia.
NC RO1 CA57789-01 (NCI)
SO J Virol, (1994 Feb) 68 (2) 619-25.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals; Cancer Journals
EM 9404

L5 ANSWER 21 OF 56 MEDLINE
AN 94047301 MEDLINE
TI Efficient self-assembly of ***human*** ***papillomavirus*** type 16 ***L1*** and ***L1*** -L2 into virus-like particles.
AU Kirnbauer R; Taub J; Greenstone H; Roden R; Durst M; Gissmann L; Lowy D R; Schiller J T
CS Laboratory of Cellular Oncology, National Cancer Institute, Bethesda, Maryland 20892.
SO J Virol, (1993 Dec) 67 (12) 6929-36.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9402

L5 ANSWER 22 OF 56 MEDLINE
AN 94040814 MEDLINE
TI Translational properties of the ***human*** ***papillomavirus*** type-6 ***L1*** -coding mRNA.
AU Tomita Y; Simizu B
CS Department of Microbiology, School of Medicine, Chiba University, Japan.
SO Gene, (1993 Nov 15) 133 (2) 223-5.
Journal code: FOP. ISSN: 0378-1119.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9402

L5 ANSWER 23 OF 56 MEDLINE
AN 93331703 MEDLINE
TI ***HPV*** -1 capsids expressed in vitro detect human serum antibodies associated with foot warts.
AU Carter J J; Hagensee M; Taflin M C; Lee S K; Koutsky L A; Galloway D A
CS Fred Hutchinson Cancer Research Center, Seattle, Washington 98104-2029.
SO Virology, (1993 Aug) 195 (2) 456-62.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9310

L5 ANSWER 24 OF 56 MEDLINE
AN 93242749 MEDLINE
TI Glycosylation of ***human*** ***papillomavirus*** type 16 ***L1*** protein.
AU Zhou J; Sun X Y; Frazer I H
CS Papillomavirus Research Unit, Princess Alexandra Hospital, Brisbane Qld., Australia.

SO Virology, (1993 May) 194 (1) 210-8.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9307

L5 ANSWER 25 OF 56 MEDLINE
AN 93188142 MEDLINE
TI Expression of ***human*** ***papillomavirus*** type 11 ***L1*** protein in insect cells: in vivo and in vitro assembly of viruslike particles.
AU Rose R C; Bonnez W; Reichman R C; Garcea R L
CS Department of Medicine, University of Rochester School of Medicine and Dentistry, New York 14642.
NC AI-82509 (NIAID)
CA37667 (NCI)
SO J Virol, (1993 Apr) 67 (4) 1936-44.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9306

L5 ANSWER 26 OF 56 MEDLINE
AN 93101691 MEDLINE
TI Papillomavirus ***L1*** major capsid protein self-assembles into virus-like particles that are highly immunogenic.
AU Kirnbauer R; Booy F; Cheng N; Lowy D R; Schiller J T
CS Laboratory of Cellular Oncology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.
SO Proc Natl Acad Sci U S A, (1992 Dec 15) 89 (24) 12180-4.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9303

L5 ANSWER 27 OF 56 MEDLINE
AN 93100811 MEDLINE
TI Self-assembly of ***human*** ***papillomavirus*** type 1 capsids by expression of the ***L1*** protein alone or by coexpression of the ***L1*** and L2 capsid proteins.
AU Hagensee M E; Yaegashi N; Galloway D A
CS Fred Hutchinson Cancer Research Center, Seattle, Washington 98104-2092.
NC P01 CA42792 (NCI)
T32 AI07044 (NIAID)
SO J Virol, (1993 Jan) 67 (1) 315-22.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9303

L5 ANSWER 28 OF 56 MEDLINE
AN 92351557 MEDLINE
TI Definition of linear antigenic regions of the HPV16 ***L1*** capsid protein using synthetic virion-like particles.
AU Zhou J; Sun X Y; Davies H; Crawford L; Park D; Frazer I H
CS Papillomavirus Research Unit, University of Queensland, Princess Alexandra Hospital, Australia.
SO Virology, (1992 Aug) 189 (2) 592-9.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9211

L5 ANSWER 29 OF 56 MEDLINE
AN 92306103 MEDLINE
TI Seroreactivity to ***HPV*** -16 proteins in women with early cervical neoplasia.
AU Barber S R; Werdel J; Symbula M; Williams J; Burkett B A; Taylor P T; Roche J K; Crum C P
CS Department of Pathology, University of Virginia Medical Center, Charlottesville.
NC CA 47676 (NCI)
AI00628 (NIAID)
SO Cancer Immunol Immunother, (1992) 35 (1) 33-8.
Journal code: CN3. ISSN: 0340-7004.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9210

L5 ANSWER 30 OF 56 MEDLINE
AN 92138066 MEDLINE
TI Detection of antibodies to a linear epitope on the major coat protein (***L1***) of ***human*** ***papillomavirus*** type-16 (***HPV*** -16) in sera from patients with cervical intraepithelial neoplasia and children.
AU Cason J; Kambo P K; Best J M; McCance D J
CS Richard Dimbleby Laboratory of Cancer Virology, Rayne Institute, St Thomas's Hospital, London, UK.
SO Int J Cancer, (1992 Feb 1) 50 (3) 349-55.
Journal code: GQU. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9205

L5 ANSWER 31 OF 56 MEDLINE
AN 92084123 MEDLINE
TI The hygromycin-resistance-encoding gene as a selection marker for vaccinia virus recombinants.
AU Zhou J; Crawford L; Sun X Y; Frazer I H
CS Department of Medicine, Princess Alexandra Hospital, Woolloongabba, Australia.

SO Gene, (1991 Nov 15) 107 (2) 307-12.
Journal code: FOP. ISSN: 0378-1119.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9203

L5 ANSWER 32 OF 56 MEDLINE
AN 92074226 MEDLINE
TI Identification of the nuclear localization signal of ***human*** ***papillomavirus*** type 16 ***L1*** protein.
AU Zhou J; Doorbar J; Sun X Y; Crawford L V; McLean C S; Frazer I H
CS Department of Medicine, University of Queensland, Princess Alexandra Hospital, Brisbane, Australia.
SO Virology, (1991 Dec) 185 (2) 625-32.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9203

L5 ANSWER 33 OF 56 MEDLINE
AN 92024081 MEDLINE
TI Expression of vaccinia ***recombinant*** ***HPV*** 16 ***L1*** and L2 ORF proteins in epithelial cells is sufficient for assembly of ***HPV*** virion-like particles.
AU Zhou J; Sun X Y; Stenzel D J; Frazer I H
CS Lions Human Immunology Laboratory, Princess Alexandra Hospital, Brisbane, Queensland, Australia.
SO Virology, (1991 Nov) 185 (1) 251-7.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9201

L5 ANSWER 34 OF 56 MEDLINE
AN 91335786 MEDLINE
TI Type-specific and cross-reactive epitopes in ***human*** ***papillomavirus*** type 16 capsid proteins.
AU Beiss B K; Heimer E; Felix A; Burk R D; Ritter D B; Mallon R G; Kadish A S
CS Department of Pathology, Albert Einstein College of Medicine, Bronx, New York 10461.
NC CA-47630 (NCI)
CA-13330 (NCI)
CA-09173 (NCI)
SO Virology, (1991 Sep) 184 (1) 460-4.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9111

L5 ANSWER 35 OF 56 MEDLINE
AN 91330163 MEDLINE
TI Binding by immunoglobulin to the ***HPV*** -16-derived proteins ***L1*** and E4 in cervical secretions of women with ***HPV*** -related cervical disease.
AU Snyder K A; Barber S R; Symbula M; Taylor P T; Crum C P; Roche J K
CS Department of Pathology, University of Virginia Health Sciences Center, Charlottesville 22908.
NC CA47676 (NCI)
DK35182 (NIDDK)
DK42358 (NIDDK)
+
SO Cancer Res, (1991 Aug 15) 51 (16) 4423-9.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9111

L5 ANSWER 36 OF 56 MEDLINE
AN 91301833 MEDLINE
TI Occurrence of antibodies to ***L1*** , L2, E4 and E7 gene products of ***human*** ***papillomavirus*** types 6b, 16 and 18 among cervical cancer patients and controls.
AU Kochel H G; Monazahian M; Sievert K; Hohne M; Thomssen C; Teichmann A; Arendt P; Thomssen R
CS University Center of Hygiene and Human Genetics, Dept. of Medical Microbiology, Gottingen, Germany.
SO Int J Cancer, (1991 Jul 9) 48 (5) 682-8.
Journal code: GQU. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9110

L5 ANSWER 37 OF 56 MEDLINE
AN 91220714 MEDLINE
TI Antibodies to ***human*** ***papillomavirus*** type-16 in human sera as revealed by the use of prokaryotically expressed viral gene products.
AU Kochel H G; Sievert K; Monazahian M; Mittelstadt-Deterding A; Teichmann A; Thomssen R
CS Centre of Hygiene and Human Genetics of the University, Department of Medical Microbiology, Gottingen, Germany.
SO Virology, (1991 Jun) 182 (2) 644-54.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9108

L5 ANSWER 38 OF 56 MEDLINE
AN 91220701 MEDLINE
TI Expression of ***human*** ***papillomavirus*** proteins in yeast Saccharomyces cerevisiae.

AU Carter J J; Yaegashi N; Jenison S A; Galloway D A
CS Fred Hutchinson Cancer Research Center, Seattle, Washington 98104.
NC CA 42792 (NCI)
CA 35568 (NCI)
CA01391 (NCI)
SO Virology, (1991 Jun) 182 (2) 513-21.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9108

L5 ANSWER 39 OF 56 MEDLINE
AN 91196248 MEDLINE
TI The open reading frame L2 of cottontail rabbit papillomavirus contains antibody-inducing neutralizing epitopes.
AU Christensen N D; Kreider J W; Kan N C; DiAngelo S L
CS Department of Pathology, Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033.
NC CA47622 (NCI)
SO Virology, (1991 Apr) 181 (2) 572-9.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9107

L5 ANSWER 40 OF 56 MEDLINE
AN 91134982 MEDLINE
TI The induction of cytotoxic T-lymphocyte precursor cells by ***recombinant*** vaccinia virus expressing ***human*** ***papillomavirus*** type 16 ***L1*** .
AU Zhou J A; McIndoe A; Davies H; Sun X Y; Crawford L
CS Department of Pathology, University of Cambridge, United Kingdom.
SO Virology, (1991 Mar) 181 (1) 203-10.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9105

L5 ANSWER 41 OF 56 MEDLINE
AN 91073131 MEDLINE
TI Definition of murine T helper cell determinants in the major capsid protein of ***human*** ***papillomavirus*** type 16.
AU Davies D H; Hill C M; Rothbard J B; Chain B M
CS Department of Biology, University College London, U.K.
SO J Gen Virol, (1990 Nov) 71 (Pt 11) 2691-8.
Journal code: I9B. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9103

L5 ANSWER 42 OF 56 MEDLINE
AN 91011369 MEDLINE
TI Increased antibody responses to ***human*** ***papillomavirus*** type 16 ***L1*** protein expressed by ***recombinant*** vaccinia virus lacking serine protease inhibitor genes.
AU Zhou J; Crawford L; McLean L; Sun X Y; Stanley M; Almond N; Smith G L
CS Department of Pathology, University of Cambridge, U.K.
SO J Gen Virol, (1990 Sep) 71 (Pt 9) 2185-90.
Journal code: I9B. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9101

L5 ANSWER 43 OF 56 MEDLINE
AN 90357770 MEDLINE
TI Coexpression of the ***human*** ***papillomavirus*** type 16 E4 and ***L1*** open reading frames in early cervical neoplasia.
AU Crum C P; Barber S; Symbula M; Snyder K; Saleh A M; Roche J K
CS Department of Pathology, University of Virginia Health Sciences Center, Charlottesville 22908.
NC CA-47676 (NCI)
DK35182 (NIDDK)
AI00628 (NIAID)
SO Virology, (1990 Sep) 178 (1) 238-46.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9011

L5 ANSWER 44 OF 56 MEDLINE
AN 90347836 MEDLINE
TI Prevalence of antibodies to ***human*** ***papillomavirus*** type 8 in human sera.
AU Steger G; Olszewsky M; Stockfleth E; Pfister H
CS Institut fur Klinische und Molekulare Virologie, Friedrich-Alexander Universitat, Erlangen, Federal Republic of Germany.
SO J Virol, (1990 Sep) 64 (9) 4399-406.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9011

L5 ANSWER 45 OF 56 MEDLINE
AN 90338478 MEDLINE
TI Production and characterisation of a monoclonal antibody to ***human*** ***papillomavirus*** type 16 using ***recombinant*** vaccinia virus.
AU McLean C S; Churcher M J; Meinke J; Smith G L; Higgins G; Stanley M; Minson A C
CS Department of Pathology, University of Cambridge.

SO J Clin Pathol, (1990 Jun) 43 (6) 488-92.
Journal code: HT3. ISSN: 0021-9746.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 9011

L5 ANSWER 46 OF 56 MEDLINE
AN 90285544 MEDLINE
TI Evidence of prevalent genital-type ***human*** ***papillomavirus*** infections in adults and children.
AU Jenison S A; Yu X P; Valentine J M; Koutsky L A; Christiansen A E; Beckmann A M; Galloway D A
CS Fred Hutchinson Cancer Research Center, Seattle, WA 98104.
NC CA 35568 (NCI)
CA 42792 (NCI)
CA 50491 (NCI)
+
SO J Infect Dis, (1990 Jul) 162 (1) 60-9.
Journal code: IH3. ISSN: 0022-1899.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 9009

L5 ANSWER 47 OF 56 MEDLINE
AN 90177203 MEDLINE
TI Immunological cross-reactivity to laboratory-produced ***HPV*** -11 virions of polysera raised against bacterially derived fusion proteins and synthetic peptides of ***HPV*** -6b and ***HPV*** -16 capsid proteins.
AU Christensen N D; Kreider J W; Cladel N M; Galloway D A
CS Department of Pathology, Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033.
NC CA47622 (NCI)
CA42791 (NCI)
CA35568 (NCI)
SO Virology, (1990 Mar) 175 (1) 1-9.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9006

L5 ANSWER 48 OF 56 MEDLINE
AN 90063546 MEDLINE
TI Identification of immunogenic regions of the major coat protein of ***human*** ***papillomavirus*** type 16 that contain type-restricted epitopes.
AU Cason J; Patel D; Naylor J; Lunney D; Shepherd P S; Best J M; McCance D J
CS Richard Dimbleby Laboratory of Cancer Virology, St Thomas' Campus, London, U.K.
SO J Gen Virol, (1989 Nov) 70 (Pt 11) 2973-87.
Journal code: I9B. ISSN: 0022-1317.

CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9003

L5 ANSWER 49 OF 56 MEDLINE
AN 89279235 MEDLINE
TI Expression in Escherichia coli of seven DNA fragments comprising the complete ***L1*** and L2 open reading frames of ***human*** ***papillomavirus*** type 6b and localization of the 'common antigen' region.
AU Strike D G; Bonnez W; Rose R C; Reichman R C
CS Department of Medicine, University of Rochester School of Medicine and Dentistry, New York 14642.
NC AI-23418
AI-32510
SO J Gen Virol, (1989 Mar) 70 (Pt 3) 543-55.
Journal code: I9B. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 8909

L5 ANSWER 50 OF 56 MEDLINE
AN 89095010 MEDLINE
TI Human antibodies react with an epitope of the ***human*** ***papillomavirus*** type 6b ***L1*** open reading frame which is distinct from the type-common epitope.
AU Jenison S A; Yu X P; Valentine J M; Galloway D A
CS Fred Hutchinson Cancer Research Center, Seattle, Washington 98104.
NC PO1-CA42792
RO1-CA35568
SO J Virol, (1989 Feb) 63 (2) 809-18.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals

EM 8904

L5 ANSWER 51 OF 56 MEDLINE
AN 88258469 MEDLINE
TI Analysis of the ***L1*** gene product of ***human*** ***papillomavirus*** type 16 by expression in a vaccinia virus ***recombinant*** .
AU Browne H M; Churcher M J; Stanley M A; Smith G L; Minson A C
CS Department of Pathology, University of Cambridge, U.K.
SO J Gen Virol, (1988 Jun) 69 (Pt 6) 1263-73.
Journal code: I9B. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 8810

L5 ANSWER 52 OF 56 MEDLINE
AN 88219535 MEDLINE
TI Detection of ***human*** ***papillomavirus*** capsid antigens in various squamous epithelial lesions using antibodies directed against the ***L1*** and L2 open reading frames.
AU Firzlaff J M; Kiviat N B; Beckmann A M; Jenison S A; Galloway D A
CS Fred Hutchinson Cancer Research Center, Seattle, Washington 98104.
NC PO1-CA42792
RO1-CA35568
SO Virology, (1988 Jun) 164 (2) 467-77.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 8808

L5 ANSWER 53 OF 56 MEDLINE
AN 88215042 MEDLINE
TI Identification of immunoreactive antigens of ***human*** ***papillomavirus*** type 6b by using Escherichia coli-expressed fusion proteins.
AU Jenison S A; Firzlaff J M; Langenberg A; Galloway D A
CS Fred Hutchinson Cancer Research Center, Seattle, Washington 98104.
NC PO1-CA42792
RO1 CA35568
SO J Virol, (1988 Jun) 62 (6) 2115-23.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 8808

L5 ANSWER 54 OF 56 MEDLINE
AN 88089510 MEDLINE
TI Expression of ***human*** ***papillomavirus*** type 6 and type 16 capsid proteins in bacteria and their antigenic characterization.
AU Banks L; Matlashewski G; Pim D; Churcher M; Roberts C; Crawford L
CS Department of Biochemical Virology, Wellcome Research Laboatories, Kent, U.K.
SO J Gen Virol, (1987 Dec) 68 (Pt 12) 3081-9.
Journal code: I9B. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 8804

L5 ANSWER 55 OF 56 MEDLINE
AN 88056332 MEDLINE
TI Expression of ***human*** ***papillomavirus*** type 6 E1, E2, ***L1*** and L2 open reading frames in Escherichia coli.
AU Thompson G H; Roman A
CS Indiana University School of Medicine, Department of Microbiology and Immunology, Indianapolis 46223.
NC AI20110

SO Gene, (1987) 56 (2-3) 289-95.
Journal code: FOP. ISSN: 0378-1119.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 8803

L5 ANSWER 56 OF 56 MEDLINE
AN 87207679 MEDLINE
TI Expression of the ***human*** ***papillomavirus*** type 6b L2 open reading frame in Escherichia coli: L2-beta-galactosidase fusion proteins and their antigenic properties.
AU Tomita Y; Shirasawa H; Sekine H; Simizu B
SO Virology, (1987 May) 158 (1) 8-14.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 8708

=> d his

(FILE 'HOME' ENTERED AT 14:44:17 ON 12 SEP 95)

FILE 'MEDLINE' ENTERED AT 14:44:36 ON 12 SEP 95
L1 4899 S ("L1")/AB,BI
L2 5129 S (HUMAN PAPILLOMAVIRUS)/AB,BI OR (HPV)/AB,BI
L3 223 S L1 AND L2
L4 82383 S RECOMBINANT/AB,BI
L5 56 S L3 AND L4

=> d l5 38 all

L5 ANSWER 38 OF 56 MEDLINE
AN 91220701 MEDLINE
TI Expression of ***human*** ***papillomavirus*** proteins in yeast Saccharomyces cerevisiae.
AU Carter J J; Yaegashi N; Jenison S A; Galloway D A
CS Fred Hutchinson Cancer Research Center, Seattle, Washington 98104.
NC CA 42792 (NCI)
CA 35568 (NCI)
CA01391 (NCI)
SO Virology, (1991 Jun) 182 (2) 513-21.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9108
AB The ***L1*** and L2 proteins of ***human*** ***papillomavirus*** (***HPV***) types 1, 6, and 16 and the E6 and E7 proteins of ***HPV*** 16 were expressed in Saccharomyces cerevisiae. The yeast expressed proteins were readily detected by immune blotting and were generally intact. The ***HPV*** 1

L1 and L2 proteins expressed in yeast were indistinguishable from the major and minor capsid proteins purified from ***HPV*** 1 virions as judged by gel electrophoresis and immunoblotting. The ***HPV*** 6 and ***HPV*** 16 L2 proteins and ***HPV*** 16 E7 proteins were secreted from yeast by fusion to the yeast pre-pro-alpha-factor leader sequence. Following secretion of the ***HPV*** 16 E7 protein a rapid method of purification was developed. The yeast expressed proteins were used as antigen targets to study the human immune response in Western blot assay, ELISA, and immune precipitation. One human serum reacted with intact, but not denatured ***HPV*** 16 L2 proteins, suggesting that the yeast expressed proteins will be useful to detect antibodies reactive with conformational epitopes.

CT Check Tags: Human; In Vitro; Support, U.S. Gov't, P.H.S.
Antibodies, Viral: IM, immunology
*Antigens, Viral: GE, genetics
Cloning, Molecular
Gene Expression
Glycoproteins: GE, genetics
Glycosylation
Molecular Weight
*Papillomavirus: GE, genetics
Papillomavirus: IM, immunology
Polymerase Chain Reaction
Precipitin Tests
Protein Processing, Post-Translational
*** Recombinant Proteins: GE, genetics***
*** Recombinant Proteins: ME, metabolism***
Saccharomyces cerevisiae: GE, genetics
*Viral Proteins: GE, genetics
Viral Proteins: IM, immunology

CN 0 (Antibodies, Viral); 0 (Antigens, Viral); 0 (Glycoproteins); 0 (***Recombinant*** Proteins); 0 (Viral Proteins)

GEN ***L1*** ; L2; E6; E7

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